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DEVELOPMENT OF TUBERCULOSIS IN ADULT LIFE

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BENEDICT TRACH, B.S.

MINNEAPOLIS

When the words phthisis and consumption were employed by Hippocrates, they designated exactly what the physician saw when he made the diagnosis. Later, when it was known that the disease usually exists for a long time before the body visibly wastes away, the word tuberculosis was coined. This word is all inclusive and in the light of recent observations may be applied to the disease from the time the neutrophils first phagocytose tubercle bacilli until the death of the host results.

Until recently physicians were unwilling to make a diagnosis of tuberculosis until clinical manifestations were present, such as symptoms and abnormal physical signs, with roentgen findings, or until the laboratory methods revealed tubercle bacilli in the sputum or pleural effusion or elsewhere. Although diagnoses based on these criteria were made far earlier in the course than those in the time of Hippocrates and for many centuries thereafter, they usually indicated that the disease had been present for a long time, and in from 80 to 85 per cent of the cases the disease had reached a moderate or far advanced stage.

It is now known that the first attack of the tubercle bacillus is on the neutrophil, since it is this cell which first phagocytoses the bacillus. The polysaccharide content of the bacillus is toxic to the neutrophil, and although this is a single cell, the destruction in the body begins with the "illness and death" of the neutrophil. Therefore, the first skirmish results in defeat for the human body. No sooner do the toxic effects to

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(Footnote continued on next page)

the neutrophils become manifest, however, than the second line of defense makes its appearance. This consists of the monocytes, which surround the ill, dead and distintegrating neutrophils and ingest them and the tubercle bacilli which they contain. There is nothing in the chemistry of the tubercle bacillus which destroys the monocytes. However, the phosphatide content of the bacillus apparently causes their conversion into epithelioid cells. While some bacilli may die in the epithelioid cells, others not only remain alive but also multiply. Later, lymphocytes are attracted to the site of the developing tubercle.

It is possible that the differential leukocyte counts of the peripheral blood may be found to give some evidence of the developing tubercle. An attempt is now being made to determine whether the increase in neutrophils, followed by an increase in monocytes and later by an increase in lymphocytes, is sufficient to be demonstrated in the peripheral blood in a recently exposed subject who has actually become infected with tubercle bacilli. While such changes in the leukocytes are not specific for tuberculosis, in the absence of other conditions which cause them and in the presence of recent exposure they are suggestive when demonstrated.

The waxes of the tubercle bacilli stimulate the proliferation of fibroblasts, while their acetone-soluble fat causes proliferation of all local connective tissue cells. This results in the laying down of fibrous tissue around the periphery of the tubercle. In many cases lime salts are deposited in the small caseous centers and in the capsule, while in about 25 per cent true bone is laid down in the capsule.[1] Thus, a temporary victory is won by the body; but unfortunately the bacilli remain alive, and the fibrous and even the bony capsules surrounding them may rupture or later be resorbed,[1] thus setting free these living and virulent micro-organisms.

After a period of from three to seven weeks [2] of tubercle formation enough tuberculoprotein has been liberated by the bacilli, through disintegration and other processes, to result in sensitization of the tissues to this substance. Up to this time there has been no way of determining the presence of tubercle bacilli and tubercle formation in the body. There are no symptoms or abnormal physical signs, the tuberculin test is negative and roentgenograms give no aid. Indeed, before sensitization appears, tubercle formation is sufficiently under way to control the tubercle bacilli at least temporarily and often for the lifetime of the patient.

Oregon Tuberculosis Association, Portland, Ore., April 2, 1936, and the California Tuberculosis Association, Sacramento, Calif., on April 3, 1936.

1. Sweany, Henry: Studies on the Pathogenesis of Primary Tuberculous Infection, Am. Rev. Tuberc. **27**:559, 1933.

2. Wallgren, Arvid: Primary Pulmonary Tuberculosis in Childhood, Am. J. Dis. Child. **49**:1105 (May) 1935.

After sensitization is established a most valuable diagnostic aid is available, in that tuberculin or pure tuberculoprotein applied to an abrasion of the skin or administered intracutaneously results in a reaction which reveals the presence of sensitization to tuberculoprotein. As far as is known, there is nothing which is taken into the body which results in such sensitization except tubercle bacilli which have caused tubercle formation.[3] Thus, a positive reaction to tuberculin is highly diagnostic of the first infection type of tuberculosis somewhere in the body.

At one time it was thought that the first infection type of tuberculosis is established in a high percentage of children before the period of adolescence. This probably was true in many places and apparently is still true in a few densely populated centers, such as Philadelphia.[4] However, throughout the greater part of the United States and in some other parts of the world the campaign against tuberculosis in man and animals has so greatly reduced or controlled the number of cases of communicable tuberculosis in both man and animals that large numbers of children now grow to adult life without having had the first infection type of tuberculosis. Indeed, in a few places the situation has been so completely reversed that, although formerly from 90 to 95 per cent of the young adults had been infected, now only from 5 to 10 per cent react positively to the tuberculin test.[5] In Norway Heimbeck[6] found that 52 per cent of the students entering a school of nursing reacted negatively to the test. A similar percentage of negative reactors was found in other groups in the same age period. In the part of the French army recently tested as many as 42 per cent of the soldiers reacted negatively to tuberculin.[7] In our testing of student nurses during the period of probation in recent years we have frequently found that less than 10 per cent react positively to the tuberculin test.[8] Thus, large numbers of persons are now reared through infancy and child-

3. Baldwin, E. R.: Studies in Immunity to Tuberculosis: I. Hypersusceptibility or Anaphylaxis, J. M. Research **22**:189, 1910. Krause, Allen K.: Factors in the Pathogenesis of Tuberculosis, Am. Rev. Tuberc. **18**:208, 1928.

4. Hetherington, H. W.; McPhedran, F. M.; Landis, H. R. M., and Opie, Eugene L.: A Survey to Determine the Prevalence of Tuberculous Infection in School Children, Am. Rev. Tuberc. **20**:421, 1929.

5. Fourth Annual Report of the Tuberculosis Committee of the American Student Health Association, Journal-Lancet **55**:350 (June 1) 1935.

6. Heimbeck, J.: Immunity to Tuberculosis, Arch. Int. Med. **41**:336 (March) 1928.

7. Tuberculin Testing of the French Army, Paris letter, M. Rec. **142**:524, 1935.

8. Myers, J. A.; Diehl, H. S., and Lees, H. D.: The Student Nurse and Tuberculosis, J. A. M. A. **102**:2086 (June 23) 1934.

hood and pass into adult life without having even the first infection type of tuberculosis.

With the decrease in the incidence of positive reactors among children and young adults in many parts of this country, there has occurred a decrease in the morbidity and mortality from tuberculosis. It has been pointed out that in some schools of nursing in recent years all the students who reacted negatively to tuberculin as probationers reacted positively at the time of graduation.[9] If all uninfected students become infected during the course of their training, it seems probable that those who were infected previous to training are reinfected. Therefore, with approximately 100 per cent of the students contaminated with tubercle bacilli during the course of their training, one must expect the incidence of demonstrable lesions, which subsequently develop, to be much higher than in a general population, in which not more than from 10 to 30 per cent of the young adults have been infected with tubercle bacilli. Where actual observations have been made this has been found to be true.

Great fear has been expressed by some authors that since the so-called protective doses of tubercle bacilli did not reach the bodies of these young adults in the period of infancy or childhood, when they become infected in schools of nursing and medicine, very serious forms of disease will develop.[10] Others have asked what actually occurs in such uninfected subjects if they become contaminated with tubercle bacilli for the first time in adult life. Does a more severe form of tuberculosis develop, and do the lesions respond to treatment in a different manner than those of persons who were first infected earlier in life?

In schools of nursing and medicine, where the students come in contact with tuberculous patients, in the absence of an adequate technic for dealing with contagious disease, there has in recent years been presented an opportunity to study the development of tuberculosis in young adults that is rarely equaled by animal experimentation, except that in experimental work it is possible to control the dosage and to kill an animal at any time in order to make a postmortem study. Since 1927 we have seen many students of nursing and medicine become contaminated with tubercle bacilli for the first time, the evidence of this contamination being a positive reaction to tuberculin which appeared after the student was exposed to tuberculous patients. In many of these students there has been no other manifestation of tuberculosis as yet. They are classified as having the first infection type of disease somewhere in their bodies, with the location undetermined. Among this

9. Geer, Everett K.: Tuberculosis Among Nurses, Arch. Int. Med. **49**:77 (Jan.) 1932. Heimbeck.[6] Myers, Diehl and Lees.[8]

10. Factors in the Falling Death Rate from Tuberculosis, editorial, Ann. Int. Med. **9**:1154 (Feb.) 1936.

group we have observed subjects in whom after the tissues had become sensitized lesions developed in such locations or to such an extent that they could be demonstrated by roentgenograms or other phases of the examination. None of these subjects has been observed for longer than nine years and many of them for a much shorter period. A few have been briefly reported on elsewhere.[11] In others who reacted positively to the tuberculin test when they entered, we have also seen lesions develop. Therefore, we have grouped these subjects on the basis of the tuberculin reaction, the type of lesion which subsequently developed and other factors.

GROUP 1

In the subjects in group 1 the reaction to tuberculin changed from negative to positive under our observation, and erythema nodosum appeared.

CASE 1.—In September 1931 an 18 year old freshman in a school of nursing reacted negatively to tuberculin. She again showed a negative reaction in September 1932. In February 1933 she had erythema nodosum, following which the tuberculin test was found to be strongly positive. There have been no other developments and apparently she is in excellent health at present.

CASE 2.—In January 1932 a freshman in a school of medicine reacted negatively to the tuberculin test. In March 1933 and February 1934 he still showed a negative reaction. Roentgen films of the chest in January 1932 and February 1934 showed no evidence of disease. He was on a service for tuberculous patients for three weeks in January 1935. On February 4 the tuberculin test was positive. In March 1935 he had erythema nodosum. In December 1936 a tuberculous abscess developed in the soft tissues beneath the clavicle on the right side. In February 1936 films showed no evidence of disease in either lung.

Thus, only two of the persons we have observed have come to our attention with erythema nodosum. This is in sharp contrast with the observations made by a number of authors who have reported erythema nodosum as a common development among those whose tissues have recently become sensitized to tuberculoprotein. We are cognizant of the fact that erythema nodosum is not always caused by sensitiveness to tuberculoprotein and that a number of other conditions may be responsible. However, when it appears, it is sufficiently suggestive to lead one to make a careful examination for tuberculosis. We have not regarded erythema nodosum as a clinical form of tuberculosis.

GROUP 2

In the subjects in group 2 the reaction to tuberculin changed from negative to positive, and a primary focus was demonstrated roentgenographically. No other lesions were demonstrated.

11. Myers, J. A.: (*a*) Recent Facts on Transmission of Tuberculosis, J. A. M. A. **97**:316 (Aug. 1) 1931; (*b*) Types of Tuberculous Lesions Found in Chests of Students of Nursing and Medicine, Am. Rev. Tuberc. **28**:93, 1933.

CASE 1.—In November 1928 a freshman medical student aged 22 reacted negatively to the tuberculin test. In 1931 the reaction to tuberculin was still negative. Roentgen films of the chest in March 1930 and subsequently, including Jan. 27, 1932, showed no evidence of disease. This student was working in a service for tuberculosis patients from Dec. 18, 1931, to Feb. 18, 1932. In February 1932 the tuberculin test was positive. A roentgenogram made on April 25 showed a small shadow in the first interspace on the right, as well as a similar shadow in the first interspace on the left. Twenty subsequent roentgen examinations, the last on Dec. 16, 1935, showed that the lesions had varied slightly but that throughout this period there had been some decrease in the size of the shadow. There were no symptoms, and no treatment was given.

CASE 2.—In September 1929, on beginning a five year nursing course, at the age of 20, a student showed a negative reaction to the tuberculin test. The reaction to tuberculin and the roentgenograms continued to be negative on periodic examinations. From Aug. 15 to Sept. 15, 1933, she was assigned to a service for tuberculous patients. On Jan. 23, 1934, the reaction to the tuberculin test was positive, and a roentgenogram revealed evidence of definite infiltration at the level of the first interspace on the left. Numerous films made after that, the last on Jan. 3, 1936, showed a gradual decrease of the shadow, with possible beginning calcification in the hilar region of the left lung. At no time was there any symptom of pulmonary tuberculosis. No treatment was given.

CASE 3.—In November 1928 a 23 year old freshman in a school of medicine reacted negatively to the tuberculin test. On periodic examinations the reaction continued to be negative. In December 1931 he gave intimate care to a diabetic patient who was in a far advanced stage of unsuspected pulmonary tuberculosis. In January 1932 the student showed a positive reaction to the tuberculin test. Roentgen films made in February 1932 revealed a definite infiltration in the upper lobe of the left lung, extending from the apex to the level of the second rib. The shadow remained unchanged until September 1932, when there was some evidence of resolution. On Dec. 19, 1933, there was marked clearing of the shadow. There had been no symptoms of tuberculosis, and no treatment had been given.

CASE 4.—In February 1928 a premedical student aged 22 reacted negatively to the tuberculin test. The reaction was periodically negative thereafter, including September 1931. Roentgenographic examination of the chest in January 1931 and January 1932 showed no evidence of disease. The student was assigned to a special service for tuberculous patients from Sept. 15 to Sept. 30, 1931. Three weeks later the reaction to the tuberculin test was strongly positive. At this time roentgen films of the chest revealed no evidence of disease. On May 30, 1932, there was evidence of infiltration within the circle of the first rib in the first interspace on the right side. There had been no symptoms of tuberculosis, and no treatment had been given.

CASE 5.—In October 1928 a 20 year old freshman in a school of medicine showed a negative reaction to the tuberculin test. The test was not repeated. There was said to have been a normal roentgenogram in 1930. In June 1931 a roentgenogram revealed evidence of pulmonary infiltration in the apex of the right lung and in the first interspace and in the first and second interspaces on the left. A roentgen film on Feb. 2, 1932, showed no change in the shadows, while those made in September 1934 and in January and June 1935 showed almost complete disappearance of the shadows. This man is now practicing medicine and apparently is in excellent health.

CASE 6.—In January 1931 a junior medical student aged 24 showed a negative reaction to the tuberculin test. During the next year he roomed with an intern who had a draining sinus from tuberculous cervical nodes. In February 1932 the student showed a positive reaction to the tuberculin test. A roentgenogram of the chest made on Dec. 29, 1931, showed evidence of a small density at the level of the third rib on the left side near the periphery. Subsequent films showed evidence of calcification in this area. The shadow was unchanged in a film made on Oct. 9, 1935. No symptoms had developed, and no treatment had been given.

CASE 7.—In September 1931 a 19 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. Roentgen films of the chest showed no evidence of disease in October 1931. The reaction to tuberculin continued to be negative in October 1932 and October 1933. Three weeks after being assigned to a service for tuberculous patients in September and October 1934 the student showed a strongly positive reaction to the tuberculin test. In September 1934 the roentgen film was still negative, but on May 1, 1935, there was evidence of infiltration in the upper lobe of the left lung. On July 8 there was a slight decrease in the extent of the shadow. All films subsequent to this examination, the last being made on Jan. 7, 1936, revealed practically no change in the shadow. No symptoms developed, and no treatment was given.

CASE 8.—In the fall of 1931 an 18 year old freshman in a school of nursing reacted negatively to the tuberculin test. In June 1935, after being graduated from the nursing school, the patient showed a negative reaction to the tuberculin test. Roentgen films made in February 1934 showed no evidence of disease. In May 1935 she gave intimate care as a special duty nurse to two tuberculous patients. On September 27 the reaction to the tuberculin test was positive. In October there was evidence of infiltration in the upper lobe of the left lung. All subsequent films, the last on Jan. 22, 1936, showed no change in the shadow. No symptoms developed, and no treatment was given.

CASE 9.—In September 1930 a 17 year old first year premedical student reacted negatively to the tuberculin test. The reaction was negative in April 1933 and in February 1934. The student came in contact with tuberculous patients when he was working in a service for patients with diseases of the nose and throat. He was not assigned to a special service for tuberculous patients. In February 1935 the reaction to the tuberculin test was strongly positive. On February 19 there was a small area of disease present in the lower portion of the upper lobe of the right lung. On May 21 a film showed a definite increase in the extent of the shadow in the right lung. On June 15 the shadow had decreased somewhat in size. In October and November 1935 and in January 1936 films showed no change in the appearance of the shadow. No symptoms developed and no treatment was given.

CASE 10.—In the fall of 1933 a 21 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. Roentgen films which had been taken in the fall of 1933 showed no evidence of disease. During the fall the student had some contact with tuberculous patients. About Feb. 14, 1934, she experienced pain in the left side of the chest, and a film showed an area of infiltration at the level of the first and second interspaces on the left side. This was thought to be a small area of pneumonia. The tuberculin test was not repeated at this time. On February 22 a roentgen film showed no change in the shadow. On March 16 the film showed some decrease in the size of the shadow. The student became suspicious that she had tuberculosis, and on March 14 had a tuberculin test made privately. At this time she showed a strongly positive reaction. No symptoms developed, and no treatment was given.

CASE 11.—In September 1930 a 24 year old graduate nurse, while taking a course in public health nursing, reacted negatively to the tuberculin test. A roentgen film of the chest showed no evidence of disease. In July 1932 the reaction to the tuberculin test was positive. On July 17 a roentgen film revealed definite evidence of infiltration in the first and second interspaces on the right side. On August 17 there was a slight decrease in the size of the shadow. On October 20 the shadow was unchanged. No symptoms developed, and no treatment was given.

CASE 12.—In October 1931 a 22 year old junior in a school of nursing showed a negative reaction to the tuberculin test. The reaction remained negative throughout her nursing course. On Jan. 14, 1933, a roentgen film revealed no evidence of disease. In February the student worked in a service for tuberculous patients. Three months later the tuberculin test was strongly positive. On April 28, 1933, roentgen films of the chest were negative. On August 30, 1935, a roentgen film revealed definite evidence of infiltration in the first and second interspaces near the periphery on the left side. In November 1935 and January 1936 roentgen films showed no change in the shadow. Slight pain over the upper part of the left side of the chest was the only symptom.

CASE 13.—In 1924 an 18 year old freshman in a school of nursing reacted negatively to the tuberculin test. In January 1933 she registered for graduate work in nursing, and the tuberculin test was found to be definitely positive. On February 13 there was evidence of infiltration involving the first and second interspaces on the right side. In April, June and September 1933 roentgen films revealed no change in the shadow. No symptoms developed, and no treatment was given. On March 1936 a film showed almost complete disappearance of the shadow. The nurse is now in excellent health.

CASE 14.—In 1929 a 19 year old second year premedical student reacted negatively to the tuberculin test. In November 1933 his roommate was found to have a far advanced stage of pulmonary tuberculosis. A roentgen film of the student's chest showed no evidence of disease in December 1933. On June 14, 1934, there was an area of infiltration in the left lung at the level of the third rib, midway between the periphery and the hilus. There was evidence also of definite infiltration in the hilar region. The student was institutionalized for five months. Roentgen films made on Jan. 2, 1935, showed a definite decrease in the extent of the shadow. Further decrease was observed on Feb. 18, 1935, and April 22, 1935. On Feb. 20, 1935, phrenic exeresis was performed. On June 17 the shadow was small. A roentgen film on Jan. 20, 1936, showed almost complete disappearance of the shadow.

CASE 15.—In September 1931 a 19 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. In May 1933 the tuberculin test was strongly positive. The student was assigned to a service for tuberculous patients from Sept. 15 to Nov. 1, 1934. Roentgen films of the chest made on Sept. 14, 1934, and March 26, 1935, showed no evidence of disease. On July 31, 1935, definite infiltration appeared in the apex and the first interspace on the left side. The shadow remained unchanged in films made in August, September and October 1935 and on Feb. 20, 1936. She was under treatment for four and one-half months. No symptoms developed.

CASE 16.—In 1928 an 18 year old freshman in a school of nursing reacted negatively to the tuberculin test. She worked in a service for tuberculous patients in the spring of 1932. Through October 1933 reaction to the tuberculin test remained negative. In July 1934 the reaction was definitely positive, and an area of infiltra-

tion was present in the second interspace near the periphery on the left. Elevation of the temperature and fatigue were noted. Strict rest in bed for a few weeks was ordered. At present the nurse is able to work full time.

CASE 17.—In September 1933 a 23 year old freshman in a school of nursing reacted negatively to the tuberculin test. A roentgen film of the chest made on Oct. 19, 1933, showed no evidence of disease. On April 22 she reacted positively to the tuberculin test. A roentgen film of the chest on May 8 showed evidence of a small area of infiltration at the level of the second interspace on the right side. Films made on June 18 and July 23 showed an increase in the size of the shadow. The only treatment was rest in bed. In March 1936 no change in the shadow was apparent.

CASE 18.—In September 1934 a 25 year old freshman in a school of medicine reacted negatively to the tuberculin test. Subsequently a fraternity brother who was a graduate of a medical school lived in the same house, and while there it was found that he had pulmonary tuberculosis in a communicable form. On Jan. 14, 1936, the student showed a positive reaction to the tuberculin test, and roentgenograms showed evidence of infiltration in the apex of the left lung and in the first interspace. A roentgen film on Feb. 24, 1936, showed no change in the size of the shadow.

CASE 19.—In September 1930 a 19 year old first year premedical student reacted negatively to the tuberculin test. In April 1933 the reaction to the test was positive. On July 24, 1933, and Feb. 26, 1934, roentgenograms of the chest showed no evidence of disease. On Feb. 27, 1935, there was definite evidence of infiltration in the subclavicular region on the right side. Periodic films made over the next several months showed no change. On Dec. 27, 1935, there was a slight decrease in the size of the shadow.

CASE 20.—In September 1932 a 19 year old freshman in a school of nursing reacted negatively to the tuberculin test. The reaction continued to be negative at periodic examinations. Roentgenograms of the chest on Aug. 11, 1934, showed no evidence of disease. The student worked in a service for tuberculous patients in October and November 1934, immediately after which the tuberculin test was definitely positive. On May 2, 1935, an x-ray film showed no evidence of disease. On Sept. 26, 1935, there was definite evidence of infiltration in the left lung, extending from the region of the hilus into the second and third interspaces. The shadows showed no change in October and November 1935 but were slightly decreased in extent in February 1936. No symptoms developed and no treatment was given.

CASE 21.—In September 1929 a 19 year old freshman in a school of medicine reacted negatively to the tuberculin test. The reaction continued to be negative in February 1930, February 1931 and February 1932. Roentgenograms of the chest in January 1930, January 1931 and March 1932 showed no evidence of disease. The student was assigned to a special service for tuberculous patients from Oct. 3 to 16, 1932. The reaction to the tuberculin test was still negative in February 1933, but in August 1934 it was positive. Roentgenograms made in June 1934, after slight pain had been noted in the chest and the temperature had reached 100 F. each day for ten days, revealed an area of infiltration only in the first interspace on the left side. Films made on Aug. 13, 1935, and compared with the films taken during the previous year showed a gradual decrease in the extent of the shadow in the left lung. Films made on Dec. 4, 1935, showed that there had been no change since August.

In a few cases in this group it has been impossible to determine with certainty that the shadows represented only the first infection type of tuberculosis, because the tuberculin testing was not always done with sufficient frequency. We regard any lesion that appears soon after the tissues are sensitized as representing the first infection type of the disease. However, if a year or more has elapsed between the making of the tuberculin tests, there has been ample time between the last negative and the first positive reaction for the first infection type of disease to develop and also for the reinfection type to make its appearance.

There is nothing characteristic about the shadow produced by either type with regard to density, location and other features. From the shadow alone it is impossible to differentiate between the first infection type of tuberculosis, the reinfection type of tuberculosis, pneumonia, abscess and other processes in the early course of development. It is only when the tuberculin tests have been carefully administered and the reactions interpreted with sufficient frequency or when the lesions have been observed for a sufficiently long time that it is possible to differentiate between the first infection and the reinfection type of tuberculosis.

Not all lesions of the first infection type of tuberculosis attack the lungs, and among those which do there are many that do not become sufficiently large or produce enough reaction around them to cast shadows which can be visualized by the naked eye on the x-ray film. Indeed, in the majority of young adults who become infected, it is impossible by any phase of the examination actually to locate the lesions. In this respect young adults do not differ from infants and children who become contaminated with tubercle bacilli, in whom it has been shown that under most ideal examinations it is rare to locate the lesion in as many as 25 per cent of those reacting positively to the tuberculin test at any one time.[12] Nevertheless, a definitely positive reaction to the tuberculin test is accurate evidence of the presence of tubercle formation somewhere in the body.

Obviously, since a lesion of the first infection type of tuberculosis is microscopic in the beginning a considerable period of time is required for it to grow to sufficient size to cast a shadow which can be visualized on an x-ray film. About the time the tissues become sensitized to tuberculoprotein or soon after in a small percentage of cases an inflammatory area appears around the lesion. When this area is sufficiently extensive to cast a shadow that can be visualized on the x-ray film, it is usually homogeneous in appearance over a period of many weeks or months, after which it begins to disappear. Wallgren,[2] Chown and

12. Harrington, F. E.: Childhood Type Tuberculosis: A Report of Ten Years of Activity, 1921-1931, Lymanhurst School for Tuberculous Children, Minneapolis, The Board of Public Welfare, 1932.

Medovy,[13] Reichle [14] and many others have called attention to these shadows as they appear in infancy and childhood. Attention has been called to the appearance of such lesions among young adults, particularly among students of nursing and medicine or recent graduates in these professions, by a number of workers, notably Heimbeck,[15] Rist [16] and Geer.[17] Rigler [18] has made a study of the period of time which elapses between exposure and the attainment by a lesion of sufficient size to cast a clearly visible shadow on the x-ray film.

The nature of the inflammatory reaction around the focus has been discussed elsewhere.[19] As is the case among children, none of these lesions has shown evidence of cavitation. The subjects who have been observed for a sufficiently long time have shown a definite reduction in the size of the shadows, and in some cases no evidence of disease remains. In other cases shadows remain which are interpreted as strands of fibrous tissue, and occasionally lime deposits make their appearance at the site of a previous shadow.

In the majority of these cases there have been no noticeable symptoms. In the occasional case there has been slight pain in the chest or a mild elevation of the temperature. The general absence of symptoms or the occasional presence of mild symptoms of short duration is in conformity with the findings in infants and children with the first infection type of disease.[20] Physical signs are usually entirely lacking.

Those subjects whom we have observed throughout the course of the disease have received no treatment. A few of the subjects who have come under the observation of other physicians have undergone hospitalization and interruption of the phrenic nerve. However, the ultimate results are apparently the same either with or without treatment. This does not differ from what has been found to be true for infants and children with the first infection type of tuberculosis, even

13. Chown, Bruce, and Medovy, Harry: Pulmonary Tuberculosis in Childhood, Canad. M. A. J. **29**:364, 1933.

14. Reichle, H. S.: Resolving Exudates in Pulmonary Tuberculosis of Childhood, Am. J. Dis. Child. **45**:307 (Feb.); **46**:969 (Nov.) 1933.

15. Heimbeck, J.: Ueber Infektion und Vakzination bei Tuberkulose, Med. Klin. **29**:1731, 1933.

16. Rist, E.: Opening of a Sanatorium for Students, M. Rec. **142**:522, 1935.

17. Geer, Everett K.: Primary Tuberculosis Among Nurses, Am. Rev. Tuberc. **29**:88, 1934.

18. Rigler, Leo G., and Exner, Frederick B.: The Latent Period in the Roentgen Diagnosis of Pulmonary Tuberculosis, J. A. M. A. **102**:1750 (May 26) 1934.

19. Myers, J. A.: The First-Infection Type of Tuberculosis: Its Preallergic and Postallergic Stages of Development, Am. Rev. Tuberc. **34**:317, 1936.

20. Myers, J. A.; Harrington, F. E.; Stewart, C. A., and Wulff, Marjorie: First-Infection-Type Tuberculosis: Its Treatment and Prognosis, Am. Rev. Tuberc. **32**:631, 1935.

when the lesions are extensive.[21] Thus, in our experience the subject who has avoided infection through infancy and childhood and becomes infected in adult life shows the first infection type of lesions, and these take the same benign course as similar lesions which develop in infants and children. The first infection type of tuberculosis begins to develop in tissues that are not sensitized to tuberculoprotein. The defense mechanism, consisting of leukocytes, connective tissue cells and other factors, usually causes the tubercle bacilli to be well surrounded and under at least temporary control before sensitization occurs. This reaction is far less intense than when reinfection begins development on sensitized tissues, as shown experimentally by Lemon.[22]

GROUP 3

In the subjects in group 3 the reaction to tuberculin changed from negative to positive. The primary parenchymal lesions were demonstrable roentgenographically in some cases and nondemonstrable in others. Pleural effusion also developed.

CASE 1.—In February 1930 a 22 year old freshman in a school of medicine reacted negatively to the tuberculin test. The reaction continued to be negative through October 1932. After the student had worked in a service for tuberculous patients the reaction to tuberculin became positive. On Feb. 20, 1933, pleural effusion was present on the right side, although the roentgenogram made on Feb. 10 had shown a normal picture. In June 1933 the effusion had completely absorbed, and there appeared only evidence of thickening of the pleura. In August 1933, in addition to evidence of diaphragmatic pleurisy, there was a small area of involvement in the parenchyma of the upper lobe of the right lung. In October 1933 this shadow had not changed. The lesion persisted through the remainder of 1933 and 1934 but could not be visualized in June 1935. This woman is now working full time as a resident physician in a hospital.

CASE 2.—In January 1929 a 24 year old sophomore medical student reacted negatively to the tuberculin test. The reaction continued to be negative through Jan. 5, 1931, when a roentgenogram showed no evidence of disease. He was assigned to a special service for tuberculous patients from Dec. 6, 1930, to Jan. 5, 1931, and again from March 8 to 18, 1931. The reaction to the tuberculin test was markedly positive on March 14, 1931. The roentgenogram made at that time showed no evidence of disease. On April 20 the roentgenogram revealed an area of parenchymal infiltration near the periphery in the second interspace on the right side. On June 9 a large effusion was present in the right pleural cavity. On October 26 the effusion had nearly disappeared, but the parenchymal lesion appeared unchanged. Numerous subsequent films revealed obliteration of the right costophrenic angle. On April 17, 1933, and Feb. 12, 1936, the parenchymal shadow was observed to be sharply outlined and considerably reduced in size. This man is now working full time as a physician in government service.

21. Myers, J. A.: Treatment, Prognosis and Prevention of First Infection Type of Tuberculosis, Journal-Lancet **56**:24, 1936.

22. Lemon, W. S., and Montgomery, L. G.: Pleural and Pulmonary Lesions Resulting from Intrapleural Injection into Rabbits of Mycobacterium Tuberculosis, J. Thoracic Surg. **3**:612, 1934.

CASE 3.—In November 1926 a 20 year old sophomore medical student reacted negatively to the tuberculin test. The reaction was negative throughout her entire medical course. In May 1929 the reaction became strongly positive after she had worked in a service for tuberculous patients as an intern. A roentgenogram of the chest showed a small area of infiltration in the pulmonary parenchyma near the periphery, at the level of the second interspace on the right. In May 1930 a large pleural effusion was present on the right side and persisted for several months. After that numerous roentgenograms of the chest showed obliteration of the costophrenic angle on the right. On Feb. 24, 1936, a film showed evidence of probable beginning calcification in the region of the parenchymal shadow. This woman is now married and is practicing medicine. Apparently she is in excellent health.

CASE 4.—In October 1928 a 23 year old junior medical student reacted negatively to the tuberculin test. In July 1929 the reaction was positive, a pleural effusion was present on the right side and a small parenchymal infiltration was present in the apex of the right lung. The student was hospitalized from July 17 to Nov. 14, 1929. Subsequent roentgenograms, taken through 1935, have shown evidence of thickening of the pleura over the base of the right lung, and the area of disease in the apex has become small. This man is now practicing medicine and apparently is in good health.

CASE 5.—In February 1930 a 21 year old freshman in a medical school reacted negatively to the tuberculin test. In February 1931 he showed a positive reaction to the tuberculin test. A roentgenogram of the chest made on Jan. 20, 1930, and another made on Jan. 30, 1931, showed no evidence of disease. A film made on May 5, 1931, showed pleurisy with effusion on the right side. There was a small area of infiltration at the level of the third interspace near the periphery on the right side. After the patient had spent three months at rest in bed the effusion had disappeared. The only remaining evidence of pleurisy through many subsequent examinations was thickening of the pleura over the base of the right lung. The lesion in the pulmonary parenchyma showed no change through the remainder of 1931, 1932 and 1933, including April. This man is now practicing medicine and is apparently well.

CASE 6.—In September 1930 a 19 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. A roentgenogram of the chest on Sept. 6, 1932, showed nothing abnormal. From Sept. 15 to Nov. 1, 1932, she worked in a service for tuberculous patients. On May 15, 1933, the reaction to the tuberculin test was positive, and on May 19 she had pleurisy with effusion on the right side. Practically all the fluid had absorbed by September 15. On July 6, 1933, as the fluid was absorbing, a small area of infiltration appeared in the right lung at the level of the second and third interspaces. This shadow appeared practically unchanged on films taken on September 15 and November 22. However, on November 22 a small area of infiltration was present in the first interspace on the left side. On Jan. 25, 1934, the shadow in the right lung had slightly increased in size. On July 13 the shadow in the left lung was not visible, while that in the right lung had become smaller. On November 7 both shadows were visible. On Jan. 7, 1935, the shadow in the right lung was sharply outlined, and that in the left lung was barely visible. On July 1 the shadow in the right lung had increased somewhat in extent, while that in the left lung was not visible.

CASE 7.—In January 1932 an 18 year old freshman in a college of science, literature and arts reacted negatively to the tuberculin test. During part of the time he was in college he was associated with a friend who had tubercle bacilli in the sputum. In June 1935 the student had pleurisy with effusion on the left side

and a definite area of infiltration in the upper lobe of the left lung. At this time the reaction to the tuberculin test was positive. Since then the student has been hospitalized.

CASE 8.—In March 1933 a 27 year old sophomore in a school of medicine showed a negative reaction to the tuberculin test. The reaction was negative also in 1934 and in January 1935. On April 6, 1934, roentgenograms of the chest were entirely clear. The student was assigned to a service for tuberculous patients from Jan. to Feb. 10, 1935. In April 1935 he complained of pain in the chest. On May 1 the reaction to the tuberculin test was positive, and pleural effusion was present. The effusion had entirely disappeared by Aug. 20, 1935. On December 11 there remained only evidence of slight thickening of the pleura on the left side. No treatment was given. He is now working full time as an intern and apparently is in excellent health.

CASE 9.—In 1930 a 24 year old second year premedical student showed a negative reaction to the tuberculin test. In 1931 and 1932 the reaction was still negative. Roentgenograms of the chest in February 1931 and 1932 showed no abnormality. On Feb. 21, 1933, the reaction to the tuberculin test was positive, but roentgenograms of the chest again showed nothing abnormal. The student was assigned to a service for tuberculous patients for three weeks in October 1934. Roentgenograms in March 1935 showed a normal chest, but films made in July 1935 showed evidence of pleurisy with effusion on the left side. The student was kept strictly at rest in bed until Oct. 1, 1935. On November 15 a roentgenogram revealed only evidence of previous pleurisy, with no effusion. No symptoms of a pathologic condition of the parenchyma could be visualized. This man is now practicing medicine and apparently is in good health.

CASE 10.—In May 1930 a 20 year old second year premedical student reacted negatively to the tuberculin test. The reaction was again negative in February 1931, February 1932 and February 1933. Roentgenograms of the chest in January 1931 and February 1932 revealed no evidence of disease. The student was assigned to a service for tuberculous patients for three weeks, beginning June 18, 1933. At that time the reaction to the tuberculin test was positive. Roentgenograms of the chest in February 1934 and December 1934 showed no evidence of disease. On Dec. 8, 1934, roentgenograms showed definite evidence of pleural effusion on the right side. The effusion persisted over several months, after which it absorbed, so that on Dec. 18, 1935, there was no evidence of adhesions or other remnants of the pleurisy. The chest appeared essentially normal. This man is now working full time as a resident physician.

CASE 11.—In September 1929 a 19 year old freshman in a school of nursing reacted negatively to the tuberculin test. During part of August and September she was exposed to a patient who had tuberculosis in a communicable form. In October the reaction to the tuberculin test became strongly positive, but a roentgenogram showed no evidence of disease. On Nov. 25, 1930, pleural effusion was present on the right side. After several months the fluid absorbed, and numerous roentgenograms made subsequently, the last in September 1935, showed evidence of thickening of the pleura over the base of the right lung with obliteration of the costophrenic angle. This woman is now working full time as a nurse and apparently is in good health.

CASE 12.—In September 1930 a 20 year old junior in a school of nursing showed a negative reaction to the tuberculin test. In October 1931 the reaction was still negative. In June 1932, after being exposed to tuberculosis, the student showed a positive reaction to the tuberculin test. Roentgenograms made on June

3 and Aug. 18, 1932, and March 8, April 27, Aug. 1 and Dec. 1, 1933, showed no evidence of disease. On Jan. 15, 1934, pleural effusion was present on the left side. By March 7, 1934, the effusion had disappeared, and there was evidence of thickening of the pleura with adhesions over the base of the left lung. On July 30, 1934, there was no change. This woman was last seen on Aug. 3, 1934, when she accepted a position in another state, and she was apparently in good health.

CASE 13.—In September 1932 a 22 year old student in a school of nursing reacted negatively to the tuberculin test. Roentgenograms of the chest made on Sept. 22, 1932, showed no evidence of disease. From October 1 to November 15 she was assigned to a service for tuberculous patients. On Jan. 31, 1933, the reaction to the tuberculin test was positive and pleural effusion was present on the left side. The effusion persisted through February but was definitely diminished, as shown by a roentgenogram made on March 14. By Jan. 26, 1934, the fluid had completely disappeared, and there was no evidence of its previous existence by way of thickening of the pleura or obliteration of the costophrenic angle.

CASE 14.—In September 1931 a 19 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. The reaction was again negative in October 1932. Roentgenograms of the chest in October 1932 showed no evidence of disease. In February 1933 reaction to the tuberculin test was positive, but roentgenograms of the chest showed no evidence of disease. Because of pain over the upper part of the left side of the chest, roentgenograms were made on Feb. 17, 1933, and these showed slight evidence of infiltration in the upper lobe on the left side. On March 6 pleural effusion was easily demonstrated on the left side. On April 4 the fluid had practically disappeared, but there was obliteration of the left costophrenic angle. Numerous roentgenograms since then, the last on June 6, 1935, have shown the development of a Ghon tubercle in the region of the previous infiltration on the left side, but a small area of infiltration has appeared in the extreme apex of the left lung. There have been no symptoms at any time after the pleural effusion disappeared. This woman is now working full time as a nurse and apparently is in good health.

CASE 15.—In 1925 an 18 year old freshman in a school of nursing reacted negatively to the tuberculin test. She was graduated from the school of nursing in 1928. From 1928 to 1932 she worked in a service for tuberculous patients. In June 1932 pleurisy with effusion developed on the right side, and the reaction to the tuberculin test was found to be positive. After four months the patient entered a sanatorium, where she was treated for eighteen months. In February 1936 a roentgenogram of the chest showed no evidence of disease in either lung.

CASE 16.—In September 1930 a 21 year old sophomore in a school of nursing reacted negatively to the tuberculin test. The reaction was still negative just before she entered a service for tuberculous patients from July 15 to Aug. 17, 1933. The test was not administered again until April 1934, when she was registered for a course on public health nursing; the reaction was then definitely positive. X-ray films of the chest on July 13 and Sept. 14, 1933, had showed no evidence of disease. On April 21, 1934, there was definite roentgen evidence of pleurisy at the base of the left lung, but no fluid could be demonstrated. By Jan. 18, 1935, all evidence of pleurisy had disappeared.

CASE 17.—In September 1931 a 21 year old freshman in a school of nursing reacted negatively to the tuberculin test. The reaction was still negative on Sept. 23, 1932. Roentgenograms of the chest in September 1932 showed no evidence of pulmonary disease. In January 1935, as a student in public health nursing, she showed a positive

reaction to the tuberculin test. On Jan. 28, 1935, roentgenograms of the chest revealed no evidence of disease. On April 10 a roentgenogram showed evidence of a small effusion in the right pleural cavity. The amount of fluid increased until a large effusion was present on April 16. On May 2 there was a considerable decrease in the amount of fluid. Further decrease was observed on May 10. In March 1936 there was no evidence of pleurisy.

CASE 18.—In March 1935 a 20 year old freshman in a school of agriculture reacted negatively to the tuberculin test. In 1934, when he was a high school student, the reaction to the test was negative. On March 5, 1936, evidence of pleural effusion on the right side was noted. At this time the reaction to the tuberculin test was definitely positive, but the source of exposure was unknown.

We regard pleurisy with effusion as a reinfection form of tuberculosis which develops from the focus of the first infection. The tissues are highly sensitized to tuberculoprotein through the development of the primary lesion, and bacilli are easily transmitted to the lymph channels of the visceral pleura from the lesions which often lie near the periphery of the lung. The appearance of fluid in the pleural cavity is usually preceded by pain, and friction sounds may be elicited for a few days. When effusion begins to make its appearance and ordinary anteroposterior roentgenograms will not demonstrate it with certainty, Rigler's [23] posture method is of great aid. When the effusion becomes larger, it is usually possible to recover tubercle bacilli from smears of centrifugated fluid or by culture and inoculation methods. There is usually a rise in temperature, and it often increases until it reaches 102 or 103 F. The fever may be present for only a few days, or it may persist for several weeks. In the occasional case fever is slight or absent, and no pain is experienced.

In the earlier years of our work, we aspirated nearly all the larger effusions and in some cases introduced air into the pleural cavity. More recently, however, aspiration has been practiced only when the effusion was so large as to displace the mediastinum, when pressure symptoms were present or when fever had persisted for an unduly long time. We have discontinued the use of air in the pleural cavity unless a reinfection type of lesion can be demonstrated in the lung. A period of rest in bed is usually indicated while symptoms are present, although some of our patients who for various reasons did not have such periods of rest in bed controlled the disease without complications. In none of this group of patients have we seen any complication, such as empyema.

After the effusion absorbs there may remain definite evidence of thickening of the pleura, diaphragmatic adhesions and partial or complete obliteration of the costophrenic angle. Again no abnormal finding

23. Rigler, Leo G.: Roentgen Diagnosis of Small Pleural Effusions, J. A. M. A. **96**:104 (Jan. 10) 1931.

remains; the excursion of the diaphragm is normal, and from no phase of the examination, including roentgenograms, is one able to detect any evidence of the previously existing pleurisy.

We have seen pleurisy with effusion follow rather closely the development of the first infection type of tuberculosis in infants and children, but it appears to occur more frequently in young adults who have recently been infected. It is possible that this is only apparent, because the infant or child may not be able to call attention to the pain and other symptoms, or the fever is thought to be due to ordinary respiratory infection and hence an adequate examination is not made while the effusion is present. In a group of 4,148 children who showed a negative reaction to the tuberculin test, 89 showed some evidence of pleural change. Although 30 of these children had visible interlobar pleural shadows, between either the upper or the lower and the middle lobe of the right lung, we no longer regard this as a significant finding in all cases. In 40 there was definite evidence of diaphragmatic adhesions and pleurisy over the base of one or both lungs. In 17 there was evidence of thickening of the pleura over an entire lung, suggestive of an earlier existence of pleural effusion. In 3 there was evidence of interlobar or encapsulated effusion. In another group of 1,782 children with a slightly positive reaction to tuberculin, 25 showed evidence of pleural changes, 4 of whom had only visible interlobar pleural shadows. In another group of 2,615 children with a markedly positive reaction to tuberculin, 145 showed evidence of changes in the pleura, 55 of whom had only visible interlobar pleural shadows. The remaining 90 had definite pleural changes, such as diaphragmatic adhesions and thickening of the pleura over an entire lung, and 10 had pleurisy with effusion at the time of examination.[11a]

Among the young adults reported on in this paper, more careful observations were made by the students themselves, as well as those in charge of the examinations, than for the group of children. Hence, slight symptoms, such as pain in the chest were usually reported early. One must not overlook the possibility that by the time adult life is reached foreign material may have so accumulated or resulted in such changes in the lymphatic vessels as to decrease their efficiency, thus retarding the flow of lymph and giving tubercle bacilli which reach the lymph channels in the visceral pleura a longer opportunity to gain a foothold.

GROUP 4

In the subjects in group 4 the reaction to tuberculin changed from negative to positive, and clinical pulmonary tuberculosis later made its appearance, with or without a demonstrable primary focus or pleurisy with effusion.

CASE 1.—In September 1932 an 18 year old freshman in a school of nursing reacted negatively to the tuberculin test and continued to do so through March and September 1933. A roentgenogram of the chest in July 1933 showed no evidence of disease. The reaction to the tuberculin test was positive in March 1934. On April 16 a roentgenogram showed evidence of slight infiltration in the base of the right lung. On May 1 this area had definitely increased in size. After a slight pulmonary hemorrhage and the finding of tubercle bacilli in the sputum in May 1934 artificial pneumothorax treatment was instituted, with the patient ambulatory. This student was graduated in February 1936 and is apparently in good health.

CASE 2.—In January 1931 a 17 year old first year premedical student reacted negatively to the tuberculin test. In May 1933 he had a pulmonary hemorrhage. There had been no known exposure to tuberculosis. In June 1933 he reacted positively to 1 mg. of tuberculin. On May 24 there was infiltration extending from the shadow of the clavicle to the level of the fourth rib. On May 26 the sputum contained tubercle bacilli. On June 1 artificial pneumothorax was instituted, with the student ambulatory. He has continued in medical school and apparently is in good health.

CASE 3.—In March 1932 a 20 year old freshman medical student reacted negatively to the tuberculin test and continued to do so through February 1934. Roentgenograms of the chest in March 1932 showed no evidence of disease. In November 1934 the reaction to the tuberculin test was strongly positive. Roentgenograms of the chest in February 1934 and March 1935 showed no evidence of disease. In July 1935, while working as an intern, he had a pulmonary hemorrhage. A roentgenogram on July 17 showed evidence of a large infiltration in the medial portion of the upper lobe of the right lung, with evidence of cavitation. Strict rest in bed was immediately instituted, and artificial pneumothorax was begun on the right side on July 28. The patient is still in bed but apparently is making an excellent recovery.

CASE 4.—In February 1928 a 28 year old junior in a school of dentistry reacted negatively to the tuberculin test. In April 1931 pleurisy with effusion developed on the left side. He was kept at rest in bed for several months. On Jan. 25, 1932, evidence of pleurisy with effusion was found on the right side. A small amount of fluid was still present on June 9, and there had also appeared a small area of infiltration in the first interspace on the left side. Numerous roentgenograms made since that time have shown no change in the parenchymal shadow, and there remains evidence of thickening of the pleura over the bases of both sides. At the present time this man is practicing dentistry and is apparently in good health.

CASE 5.—In September 1930 an 18 year old freshman in a school of nursing reacted negatively to the tuberculin test and continued to do so through June 1931. In May 1932 the reaction to the tuberculin test was positive. She worked in a service for tuberculous patients from Dec. 31, 1932, to Feb. 15, 1933. On April 20, 1932, a roentgenogram showed no evidence of disease. On December 29 roentgenograms revealed a small area of infiltration in the second interspace near the periphery on the left side. On May 8, 1933, the area of infiltration had extended into the third interspace on the left side, and there was some indication of beginning cavity formation. Artificial pneumothorax was then instituted on the left side, and the patient was treated in a sanatorium until Aug. 21, 1935. She continues to receive artificial pneumothorax treatment and is apparently in good health.

CASE 6.—In September 1932 a 22 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. Roentgenograms of the chest made on October 28 showed no evidence of disease. On May 15, 1933, the reaction to the tuberculin test was positive. Roentgenograms of the chest made on July 29, 1933, Feb. 28, 1934, and July 14, 1934, showed no evidence of disease. On Nov. 14, 1934, an area of infiltration was present at the level of the first interspace on the left. The student worked in a service for tuberculous patients from Nov. 15, 1934, to Jan. 2, 1935. On Jan. 2, 1935, roentgenograms revealed no change in this shadow. At this time there was a questionable area of infiltration in the right lung at the level of the third interspace. On January 7 the shadow in the left lung remained unchanged, as well as the questionable area in the right lung. On March 4 no change was evident. On April 5 the shadow in the left lung showed slight evidence of an increase in size, while that in the right lung had extended from the third to the fourth interspace. The patient was then hospitalized. In August there was a considerable increase in the extent of the shadow, and artificial pneumothorax was instituted. In December empyema developed and is still being treated by the aspiration method.

CASE 7.—In 1928 an 18 year old freshman in a school of nursing reacted negatively to the tuberculin test and continued to do so through her entire nursing course. After graduation in 1931 she did private duty nursing. In June 1935 she accepted a position in a hospital where there was considerable contact with tuberculous patients. In October 1935 roentgenograms revealed evidence of infiltration in the first and second interspaces on the right side and from the apex of the left lung to the fourth rib. On November 12 the reaction to the tuberculin test was definitely positive. This was the only test that had been administered since her graduation in 1931. No symptoms developed but strict rest in bed was instituted. On Feb. 7, 1936, there was evidence of a slight decrease in the extent of the shadow.

CASE 8.—In September 1932 an 18 year old freshman in a school of pharmacy reacted negatively to the tuberculin test. No roentgenograms were made. In November 1935 he complained of pain in the right side of the chest. A roentgenogram made on November 21 revealed evidence of extensive disease with cavity formation in the upper lobe of the right lung. Artificial pneumothorax was instituted with the patient ambulatory.

CASE 9.—In January 1928 a 20 year old freshman in a school of medicine reacted negatively to the tuberculin test. In February 1930 the test was still negative. He worked in a service for tuberculous patients from April 9 to 20, 1931. A lesion with cavity formation developed at the base of the right lung while he was serving his internship. This lesion was controlled by artificial pneumothorax.

CASE 10.—In October 1931 a 20 year old junior in a school of nursing showed a negative reaction to the tuberculin test. In October 1930 roentgenograms of the chest revealed no evidence of disease. In August and September 1933 the student worked in a service for tuberculous patients, and soon afterward the reaction to the tuberculin test became positive. A roentgenogram of the chest in October 1933 showed no evidence of disease. The student was graduated from the school of nursing in June 1933 and then married. A normal infant was born in September 1934. The woman undertook private duty nursing in May 1935 and worked continuously until January 1936, apparently being in excellent health. Early in January 1936 she observed two nodules on the calf of the left leg. She consulted a dermatologist,

who suspected the presence of tuberculosis. Roentgenograms revealed infiltration in the upper lobe of the left lung at the level of the first interspace and a similar area of disease in the upper lobe of the right lung. No symptoms referable to the lung developed, but strict rest in bed was instituted.

CASE 11.—In 1930 a 19 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. Soon after working in a service for tuberculous patients in June, July and August 1933 she showed a strongly positive reaction. Roentgenograms of the chest at that time showed no evidence of disease. However, in November and December 1933 the patient suffered considerably from pains in the chest. A roentgenogram made on Nov. 12, 1935, revealed evidence of infiltration in the left lung, extending from the apex to the fourth rib; in the right lung there was infiltration in the second interspace near the periphery. Adhesions prevented the administration of artificial pneumothorax. Strict rest in bed was instituted.

CASE 12.—In 1928 a 19 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. Subsequent tests showed a negative reaction until she had spent six weeks in a service for tuberculous patients, beginning in September 1930. The reaction to the test was then definitely positive, but a roentgenogram showed no evidence of disease. On Oct. 29, 1933, while at work, she had a frank pulmonary hemorrhage. Examination revealed definite evidence of disease, with probable cavity formation in the upper lobe of the right lung. Artificial pneumothorax was instituted with the patient ambulatory. She is now apparently in good health.

CASE 13.—In April 1928 a 21 year old second year student in a school of nursing was given a tuberculin test. Although the record of this test was lost, the nurse stated that the reaction was negative. Roentgenograms of the chest in April 1928 showed no evidence of tuberculosis. After working in a service for tuberculous patients she showed a definitely positive reaction to the tuberculin test in October 1929. On Jan. 23, 1934, a roentgenogram revealed definite evidence of infiltration extending from the apex to the third rib on the left side. Artificial pneumothorax was instituted with the patient ambulatory, but adhesions prevented the complete collapse of the area of disease. This woman is now apparently in good health.

CASE 14.—In September 1929 a 20 year old junior in a school of nursing showed a negative reaction to the tuberculin test. On October 7 a roentgenogram of the chest showed no evidence of disease. On July 24, 1931, there was evidence of thickening of the pleura on the left side, but no fluid could be demonstrated. On August 8 a slight area of infiltration was visualized in the second interspace on the left side, but the reaction to the tuberculin test was reported as negative. On November 5 another area of infiltration was visualized in the fourth interspace. On December 23 the shadows had increased somewhat in extent. Strict rest in bed was instituted, and the shadows showed no change by June 28, 1932. Rest in bed was continued, but on April 3, 1933, a definite increase in the size of the shadow was observed. In May artificial pneumothorax was attempted without success. Through July and September 1933 there was no change in the shadow. On Jan. 22, 1934, there was a slight decrease in the extent of the shadows in the left lung, but a small area of infiltration was visualized at the level of the third interspace on the right. At this time, the reaction to tuberculin was strongly positive. In October 1935 and on Jan. 7, 1936, there was no evidence of change in the shadows.

CASE 15.—In January 1933 an 18 year old freshman in a school of nursing reacted negatively to the tuberculin test. Six months later she still showed a negative reaction. In March 1934 she reacted positively. A roentgenogram made on May 24 showed no evidence of disease. Another, made on Dec. 18, 1935, revealed evidence of considerable infiltration scattered throughout the upper lobe of the right lung and diffusely throughout the left lung. Tubercle bacilli were present in the sputum. Strict rest in bed was instituted.

CASE 16.—In September 1931 a 19 year old freshman in a school of nursing reacted negatively to the tuberculin test and continued to do so through October 1932. Roentgenograms of the chest in December 1932 showed no evidence of disease. In March 1933 the reaction to the tuberculin test was positive. Roentgenograms of the chest showed no evidence of disease in April 1934. On Feb. 7, 1935, there was a definite area of infiltration occupying the apex and the first interspace on the left side. Artificial pneumothorax was instituted, with the patient ambulatory, and there has been no further development.

CASE 17.—In October 1929 a 20 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. Roentgenograms also were negative. After caring for a tuberculous patient, she showed a positive reaction to the test in September 1930. In July 1931 there was a definite area of infiltration in the first and second interspaces on the right and a smaller area in the first and second interspaces on the left. After she had rested in bed for a year roentgenograms showed evidence of a marked decrease in the extent of the shadows. She then returned to school and was later assigned to the care of a patient who was being treated for fracture and who had unsuspected communicable pulmonary tuberculosis. In March 1933 the shadow in the left lung had definitely increased in size. In April there was evidence of a small cavity in the lesion in the left lung. Artificial pneumothorax was attempted, but adhesions prevented complete collapse of the lung. However, there was sufficient collapse to justify continuation of the treatment. By May 1934 obliterative adhesions had markedly reduced the pleural space, but the shadows in the left lung were definitely decreased in size, and those in the right lung were barely visible. In January 1935 there was no change in the shadows. In November 1935 an acute illness occurred which in the beginning the family physician diagnosed as influenza. However, he later found that the lower half of the left lung was involved by tuberculous pneumonia, and there was a definite increase in the extent of the shadows previously visualized. On the right side the small shadow remained unchanged.

CASE 18.—In December 1927 a 20 year old freshman in a school of medicine reacted negatively to the tuberculin test and continued to do so through December 1930. From Nov. 20 to Dec. 1, 1930, he worked in a special service for tuberculous patients. Roentgenograms of the chest in November 1930 showed no evidence of disease. The next test, administered in April 1931, showed a definitely positive reaction. During this month the supraclavicular lymph nodes on the left side became enlarged, and biopsy revealed tuberculosis. In April 1931 a roentgenogram revealed evidence of infiltration in the apex of the left lung. In May and June this shadow remained unchanged, and an area of infiltration appeared in the apex of the right lung. By October 3 the shadow in the left lung had increased in extent. In August tuberculous epididymitis developed. In February 1932 he had tuberculous peritonitis and was hospitalized from April 1932 to June 1933. He is now employed in a hospital and apparently is in good health.

CASE 19.—In November 1927 a 23 year old sophomore in a school of medicine reacted negatively to the tuberculin test and continued to do so until the spring

of 1929, before he began working in a service for tuberculous patients. No further tests were administered until July 1933, when a definitely positive reaction was present. At this time a roentgenogram revealed no evidence of disease. Numerous films made subsequently showed no definitely abnormal shadows until May 21, 1934, when there was an area of infiltration present in the upper lobe of the right lung. No change was then observed until June 1, 1935, when an improvement was noted in the area of infiltration in the upper lobe of the right lung, but a small area of infiltration had appeared in the upper lobe of the left lung. On November 13 there was evidence of infiltration throughout the entire upper lobe on the left side, and the infiltration in the upper lobe of the right lung had increased On Jan. 6, 1936, no change could be observed in the shadows. On February 22 there was an increase in the extent of the shadows in the left lung, and tubercle bacilli were present in the sputum. Artificial pneumothorax was instituted on February 29.

Case 20.—In November 1927 a 21 year old sophomore medical student reacted negatively to the tuberculin test. In January 1930 the reaction was positive. From Dec. 6, 1930, to Jan. 5, 1931, and again from March 8 to 18, 1931, he worked in a special service for tuberculous patients. Roentgenograms of the chest on Dec. 30, 1930, showed no evidence of disease. After graduation he worked on a full time basis and apparently was in excellent health until December 1935, when roentgenograms revealed definite evidence of infiltration extending from the apex to the third rib on the right side. He is now at strict rest in bed.

Case 21.—In October 1929 a 22 year old freshman in a school of medicine reacted negatively to the tuberculin test. Roentgenograms in January 1930 and January 1931 showed no evidence of disease. He worked in a service for tuberculous patients from Dec. 11 to 23, 1932. The reaction to the tuberculin test was positive in February 1933. On February 20 a small area of infiltration appeared in the fourth interspace on the right side. In May the area of infiltration had increased somewhat in size, and there was evidence of enlargement of the peritracheal lymph nodes on the right side. In October 1933 a moderately large pleural effusion was present on the right side. The fluid had disappeared by December 19, and there remained evidence of thickening of the pleura and obliteration of the costophrenic angle. On Nov. 19, 1934, the shadow in the fourth interspace on the right side was unchanged, but a definite area of infiltration had appeared in the apex of the right lung. In January 1935 he had a pulmonary hemorrhage. Since then he has been in a sanatorium and has undergone interruption of the phrenic nerve on the right side.

Case 22.—In December 1929 a 24 year old junior in a school of medicine showed a negative reaction to the tuberculin test. He then left school to work. The next test was administered in January 1932 and showed a definitely positive reaction. Roentgenograms of the chest on March 2 and 10 showed evidence of a Ghon tubercle and calcified mediastinal lymph nodes on the right side. There was evidence also of an infiltration in the first interspace on the right side. Because of symptoms of abdominal involvement exploratory laparotomy was performed on March 15, 1932, and revealed extensive tuberculosis of the peritoneal cavity. Large caseous nodules were present and extended over the large bowel. The upper portion of the abdominal cavity seemed to show the greatest involvement, but there was no portion which was free from the process. Death occurred on May 19, 1932.

Case 23.—In February 1930 a 23 year old junior in a school of medicine showed a negative reaction to the tuberculin test. Roentgenograms made in 1926 showed no evidence of disease. In February 1931 the reaction to the tuberculin

test was positive after he had been working in a service for tuberculous patients from January 5 to 16. Roentgenograms of the chest at this time were negative. In June 1932 there was a large pleural effusion on the right side. When the effusion absorbed, there was evidence of a small infiltration in the third interspace on the right side near the periphery. No further symptoms developed until November 1933, when a profuse pulmonary hemorrhage occurred, followed by massive atelectasis of the left lung. When the atelectasis disappeared, there was evidence of a large area of tuberculous pneumonia, which was treated by artificial pneumothorax. Later, empyema developed, and after this had become sufficiently chronic, thoracoplasty was recommended. On Jan. 17, 1936, fatal pulmonary hemorrhage occurred before thoracoplasty had been attempted.

CASE 24.—In October, 1932, a 20 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. In March 1933 the reaction to the test was positive. On July 24, 1933, a small area of infiltration was visualized in the first and second interspace on the right side. In February 1934 the shadow previously observed was not visualized. On March 13, immediately after the development of symptoms similar to those of pneumonia, a roentgenogram showed a homogeneous dense shadow involving the greater part of the upper lobe on the right side. On April 9 and 14 there was evidence that the disease had spread to the base of the left lung. Artificial pneumothorax was instituted about May 1, after which all symptoms disappeared. On June 15 the left lung was under a good state of collapse, and the right lung appeared clear. This patient then returned to her home and continued treatment with her family physician. Empyema later developed, and she died on May 25, 1935.

CASE 25.—In May 1933 a 28 year old clerk in the office of a board of education reacted negatively to the tuberculin test. The summer of 1933 was spent in a home with a patient who had tuberculosis in a communicable form. On Jan 10, 1934, the clerk had a small pulmonary hemorrhage. A careful examination revealed small areas of infiltration in the apex and first interspace on the right side and in the apex of the left lung. The reaction to the tuberculin test was positive. The patient was immediately hospitalized.

It is possible that an occasional patient in this group had only the first infection type of lesion, because the tuberculin tests were not administered with sufficient frequency to permit differentiation with certainty. However, in the majority of cases sufficient time elapsed between the finding of the positive reaction to tuberculin and the development of the lesion to assure with a reasonable degree of certainty that the lesion was of the reinfection type. In some of our cases after the development of sensitiveness to tuberculin the location of the first foci of infection could not be determined. Neither did pleurisy with effusion nor any other evidence of disease become manifest until the reinfection type was detected. For example, in case 12 there was a positive reaction to tuberculin in 1930, but it was not until 1933, almost three years after her graduation, that a pulmonary hemorrhage occurred—the first manifestation of clinical disease.

Case 20 is a similar example. He was first found to react positively to the tuberculin test in January 1930, but it was not until approximately six years later that he was ill with pulmonary tuberculosis. In others

we have seen the first infection type of focus appear in the lung soon after the reaction to the tuberculin test became positive, and later the reinfection type of disease was seen to develop, as in case 17. In still others, after the reaction first became positive, we have been able to demonstrate the location of the first infection type of lesion and have seen pleural effusions develop and finally the reinfection type of disease, as in cases 21 and 23. Only 3 of these patients have died. In cases 23 and 24 tuberculous pneumonia developed, followed by empyema. In case 24 death was due to empyema; in case 23 it was due to pulmonary hemorrhage. In case 22 severe and fatal abdominal tuberculosis developed. In each of these 3 students we followed the evolution of tuberculosis from the time of exposure to tuberculous patients until death occurred from resulting lesions.

With modern methods of treatment in most of our cases the lesions are at least temporarily under control. Fortunately, through periodic roentgen examinations of subjects who show a positive reaction to tuberculin it is now possible to detect the location of chronic pulmonary lesions of the reinfection type long before symptoms appear. When such lesions are detected and are proved to be progressive, treatment should be instituted at once. Artificial pneumothorax with the patient ambulatory [24] is proving satisfactory in many cases, particularly when the disease is unilateral, and has been administered to a few patients in this group. Because of the long interval between the time of exposure to tuberculous patients, resulting in sensitization of the tissues to tuberculoprotein, and the actual development of the chronic reinfection type of lesion, most students when graduated from schools of nursing and medicine apparently are in good health; but when they are traced over a sufficiently long period, it is not unusual to find that clinical disease has developed. However, the lesions are no more severe and respond just as well to treatment as the lesions which develop in adult life among persons who were infected in infancy or childhood.

GROUP 5

In the subjects in group 5 the reaction to tuberculin was positive when our observation began, but no evidence of clinical disease could be demonstrated. Later, reinfection forms of tuberculosis made their appearance.

CASE 1.—In September 1930 an 18 year old freshman in a school of nursing reacted positively to a full milligram of tuberculin. Roentgenograms in March and August 1931 showed no evidence of disease. In June 1932 a roentgenogram

24. Myers, J. A.: Collapse Therapy and the Ambulatory Patient, J. Thoracic Surg. **3**:175, 1933. Myers, J. A., and Levine, Ida: Artificial Pneumothorax in the Treatment of Progressive Minimal Pulmonary Tuberculosis, Am. Rev. Tuberc. **31**:518, 1935; Artificial Pneumothorax: With Particular Reference to the Ambulatory Patient, J. Thoracic Surg., to be published.

revealed evidence of infiltration in the first interspace near the periphery on the left side. In July there was no change in the shadow. In September the shadow had slightly increased. In February 1933 there was a marked decrease in the size of the shadow. In April and September only slight evidence of disease remained in this area. However, in February 1934 the extent of the shadow had definitely increased, and evidence of infiltration was present in the apex of the right lung. By January 1935 improvement was again shown in the left lung, and the right remained unchanged. No change was observed in either lung in subsequent roentgenograms through December 1935.

CASE 2.—In December 1928 a 20 year old student nurse reacted positively to the tuberculin test. Roentgenograms of the chest showed visible interlobar pleura on the right side but no evidence of disease in either lung. In November 1932, after registering for a course in public health nursing, she showed definite evidence of infiltration in the apex of the left lung. In January 1933 there was no change in the appearance of the shadow. In September 1933 this woman began working as a nurse and has continued on a full time basis.

CASE 3.—In September 1930 a 25 year old junior in a school of dentistry reacted positively to the tuberculin test. On Feb. 26, 1931, a large pleural effusion was noted on the right side. By June 1931 the effusion had absorbed, and there remained only evidence of thickening of the pleura and diaphragmatic adhesions on the right side. Roentgenograms made in 1932, 1933 and 1934 showed no change in his condition.

CASE 4.—In November 1927 a 21 year old sophomore in a medical school reacted positively to the tuberculin test. He had been exposed to a brother who died of tuberculosis in 1923. Roentgenograms of the chest on March 19, 1929, showed no evidence of disease. He worked in a service for tuberculous patients from Jan. 27 to Feb. 9, 1930. In May 1934 roentgenograms revealed a small area of infiltration in the lower lobe of the right lung. On June 30 he had a pulmonary hemorrhage. At this time there was evidence of cavitation in the lower lobe of the right lung, and he was institutionalized from July 16 to October 19. Artificial pneumothorax was instituted on August 27. He changed climate from January to October 1935. Since then he has been practicing medicine and apparently is in good health.

CASE 5.—In January 1931 a 47 year old freshman in a school of medicine showed a positive reaction to the tuberculin test. Roentgenograms on Jan. 20, 1931, and Feb. 1, 1932, revealed no evidence of disease. On Feb. 28, 1933, there was definite evidence of infiltration in the left lung extending from the apex to the third rib, as well as an area of infiltration in the first interspace on the right side. In April and June 1933 roentgenograms showed no change in the shadows.

CASE 6.—In March 1932 a 21 year old freshman in a school of nursing reacted positively to the tuberculin test. Roentgenograms of the chest at that time and again in August showed no evidence of disease. In November there was evidence of a small infiltration in the apex of the right lung. In March 1933 the shadow in the right lung was unchanged. In the left lung at the level of the second interspace was a fairly large area of infiltration. On April 15, 1933, the shadow in the right lung was unchanged, but that in the left lung had definitely increased, and there was evidence of cavity formation. The sputum contained tubercle bacilli. Artificial penumothorax was instituted on the left side, and the patient was sent to a sanatorium. In April 1935 tuberculous pneumonia developed in the right lung, after which pneumothorax was discontinued on the left side; later, partial collapse was instituted on the right side. On Feb. 25, 1936, intrapleural pneumolysis was performed on the right side.

CASE 7.—In September 1932 a 21 year old freshman in a school of nursing reacted positively to the tuberculin test. Roentgenograms of the chest on Nov. 1, 1932, and Dec. 29, 1934, showed no evidence of disease. The student worked in a special service for tuberculous patients from Jan. 1 to Feb. 15, 1935. On September 24 a roentgenogram revealed an area of infiltration in the upper lobe of the left lung. On November 12 and December 10 the shadow showed no change. On Jan. 6 and Feb. 27, 1936, roentgenograms revealed no change in the shadow.

CASE 8.—In October 1932 a 20 year old freshman in a junior college reacted positively to the tuberculin test. No roentgenogram was made until Jan. 29, 1935, when there was evidence of calcium deposits in the hilar region of the right lung. There were no other abnormal findings. During the next year a sister living in the home was found to have tuberculosis in a communicable form. Roentgenograms made on Dec. 30, 1935, showed in addition to the lime deposits evidence of infiltration extending from the apex to the second rib on the right side.

CASE 9.—In 1932 a 24 year old freshman in a medical school showed a positive reaction to the tuberculin test. There was a history of tuberculous cervical adenitis in childhood, and a remaining scar was present in the cervical region on the right. A roentgenogram revealed evidence of a Ghon tubercle in the right lung, with calcified lymph nodes in the hilar region. There was evidence of diaphragmatic adhesions on the right side. On Dec. 6, 1933, a diagnosis of tuberculosis of the left kidney and tuberculosis of the left epididymis was made. Nephrectomy was performed on June 6, 1934. Examination of the chest in May 1935 showed only calcifications, as reported in 1932.

CASE 10.—In April 1932 a 21 year old junior in a school of nursing reacted positively to the tuberculin test. At that time roentgenograms of the chest revealed no evidence of disease. On May 6, 1933, a roentgenogram showed evidence of pulmonary tuberculosis involving the upper lobes of both lungs, with cavitation in the apex of the right lung. Artificial pneumothorax was instituted with the patient ambulatory, after which she worked for some time as a nurse. She was then married and has given birth to a normal infant.

CASE 11.—In September 1929 a 19 year old freshman in a school of medicine reacted positively to the tuberculin test. On Jan. 9, 1930, roentgenograms of the chest showed no evidence of disease. On March 6 pleural effusion was present on the right side and persisted through March, when the student left school. By March 17, 1931, the effusion had completely absorbed, and there was evidence of thickening of the pleura over the base of the right lung. On Feb. 8, 1935, infiltration had appeared in the apex of the right lung and in the subclavicular region. Infiltration was present in the apex of the left lung and in the first and second interspaces. In May there was no change in the shadows. On Feb. 10, 1936, the extent of the shadow in the right lung had increased, while that in the left lung showed no change. There were no symptoms at any time except when the effusion was present.

CASE 12.—On Sept. 28, 1932, a 19 year old sophomore student in a school of nursing reacted positively to the tuberculin test. On Nov. 1, 1932, and April 26, 1933, roentgenograms of the chest revealed no evidence of disease. On Sept. 19, 1934, an infiltration was present in the first interspace on the left side. This showed no change since roentgenograms were made in October 1934. In November 1934 there was a slight increase in the extent of the shadow. On March 19, 1935, the phrenic nerve on the left side was temporarily interrupted because of an increase in

the shadow. On June 9, after a small hemoptysis occurred, artificial pneumothorax was instituted on the left side. The patient is now making satisfactory progress.

CASE 13.—In March 1932 a 19 year old freshman in a school of nursing reacted positively to tuberculin. A roentgenogram made on April 8 showed no evidence of disease. She worked in a service for tuberculous patients from Nov. 8 to Dec. 24, 1934. On Nov. 13, 1934, roentgenograms showed infiltration involving the apex and first interspace on the left side. The shadow did not change through 1935, the last examination being made on Nov. 22, 1935.

CASE 14.—In September 1930 a 17 year old freshman in a school of science, literature and arts reacted positively to the tuberculin test, having been exposed to her father, who died of tuberculosis in 1932. Records elsewhere showed that the reaction to the tuberculin test was positive in 1926 and that periodic roentgenograms of the chest had revealed no evidence of disease. On May 16, 1933, a roentgenogram revealed an area of infiltration involving the apex and first interspace on the right side. Tubercle bacilli were recovered from the sputum. Artificial pneumothorax with the patient ambulatory was instituted on July 5. She has since been graduated and has registered in the graduate school. Apparently she is in good health.

CASE 15.—In October 1933 a 30 year old teacher reacted positively to the tuberculin test. A roentgenogram of the chest taken on November 4 revealed evidence of calcium deposits in the second interspace on the left. On Jan. 10, 1934, after a small pulmonary hemorrhage occurred, definite evidence of tuberculous pneumonia involving the entire upper field of the left lung was noted.

The question often arises as to whether in those students who react positively to the tuberculin test on admission to schools of nursing and medicine clinical forms of tuberculosis develop while they are in school or soon after graduation, and, if so, whether the lesions differ materially from the lesions of those who become sensitized to tuberculoprotein during the course of their training. In group 5 are included fifteen subjects, mostly students, who when first examined reacted positively to the tuberculin test but who showed no roentgen evidence of disease or only evidence of primary foci. In all of them, either while in school or soon after graduation, clinical forms of tuberculosis developed. One had pleurisy with effusion (case 3), another had renal tuberculosis (case 9) and the others had pulmonary lesions. The sixth patient was the only member of her class who reacted positively to the test in the first year of nursing. Within approximately a year she had pulmonary tuberculosis, with cavity formation, and there were tubercle bacilli in the sputum. She has since had bilateral artificial pneumothorax and intrapleural pneumolysis and at the present time is seriously ill. As far as we have been able to observe, the lesions which developed in this group have not differed in intensity or response to treatment from the lesions of those in whom clinical disease developed after the reaction to the tuberculin test had become positive while the subjects were under our observation.

One must take into consideration the small number of positive reactors who were admitted to these schools. It seems probable that some selection has been practiced among the students who already had been contaminated when they entered. For example, in the communities in which the subjects were reared other girls and boys also had become contaminated with tubercle bacilli. Those in whom pleurisy with effusion or clinical lesions developed while they were in high school in all probability were not advised by their family physicians or their parents to enter schools of nursing or medicine. Thus, for the most part only those who had previously been contaminated and who had shown no external manifestations of tuberculosis entered such schools.

GROUP 6

In the cases in group 6 no previous tuberculin tests had been made but the roentgenographic findings were negative. Later, extensive pulmonary tuberculosis developed.

CASE 1.—In December 1927 a 22 year old graduate student reported for examination because it had been found that her roommate had had far advanced tuberculosis six months previously. The tuberculin test was not administered. A roentgenogram of the chest made on December 5 revealed no evidence of disease in either lung. On March 3, 1931, when this woman was teaching, a roentgenogram revealed only a Ghon tubercle formation in the upper lobe of the right lung. On March 17, 1932, a roentgenogram revealed extensive disease in the upper field of the right lung, with evidence of cavity formation. On April 15 artificial pneumothorax with the patient ambulatory was instituted, and the treatment has been continued to the present time.

CASE 2.—On May 24, 1929, a 20 year old student in a college of science, literature and arts showed no roentgenographic evidence of disease of the lungs. The tuberculin test was not administered. He entered a law school and completed the course. On May 28, 1935, roentgenograms of the chest revealed evidence of extensive disease with cavitation involving nearly the entire left lung. In the right lung the area of infiltration extended from the apex to the third rib, with cavitation at the level of the second rib. Strict rest in bed was instituted.

CASE 3.—In November 1928 a 19 year old student nurse had roentgenograms of the chest made which were reported as negative. No tuberculin test was administered. In August 1931 she was found to have a far advanced stage of pulmonary tuberculosis involving both lungs, with tubercle bacilli in the sputum. Strict rest in bed and later bilateral artificial pneumothorax were instituted.

CASE 4.—In October 1926 a 23 year old freshman in a school of dentistry showed no roentgen evidence of disease of the lungs. The tuberculin test was not administered. During the next year he was in intimate contact with a friend who had tuberculosis. On Oct. 20, 1927, there was a definite area of infiltration in the second interspace on the right. On April 25, 1931, a roentgenogram revealed evidence of disease involving the first and second interspaces on the right side, with cavity formation. Tubercle bacilli were present in the sputum. Artificial pneumothorax treatment with the patient ambulatory was instituted on July 3, 1931, and was discontinued on Oct. 21, 1935. Now this man is apparently in good health and is enrolled as a medical student at the age of 33.

The statement is occasionally made that during the teen age period roentgenograms of the chest will reveal evidence of any disease which may cause illness at a later time in life. However, in each of the four cases (the respective ages being 22, 29, 19 and 23 years) in group 6 the roentgenograms were entirely clear, yet several years later in each case an advanced stage of pulmonary tuberculosis developed. It now appears obvious that tuberculosis may develop in persons of any age. Any one who escapes infection as a child may become infected through contact exposure, and clinical disease may develop at any subsequent time.

In the accompanying table we have partially summarized the course of events in the 85 cases reported in this paper. It will be observed that neither meningitis nor miliary disease occurred among our patients.

Data

No. of Cases	Reaction to Tuberculin		X-Ray Findings	
	Initial	Subsequent	Initial	Final
2	Negative	Positive	Negative	Negative; had erythema nodosum
21	Negative	Positive	Negative	First infection foci
8	Negative	Positive	Negative	First infection foci with pleural effusion
10	Negative	Positive	Negative	Pleural effusion only
25	Negative	Positive	Negative	Reinfection pulmonary tuberculosis
15	Positive	.....	Negative	Reinfection pulmonary tuberculosis
4	No record	Positive	Negative	Reinfection pulmonary tuberculosis
85				

CONCLUSIONS

Young adults who have not been previously infected with tubercle bacilli become contaminated in large numbers during their course of training in some schools of nursing and medicine.

A positive reaction to tuberculin in a person who has previously shown no reaction to the test is the first obtainable evidence of the presence of tubercle formation in the body.

A few weeks is usually required after tubercle formation begins before the tissues are sufficiently sensitized to tuberculoprotein to react positively to tuberculin.

At the time the reaction to the tuberculin test first becomes positive there usually is no external manifestation of tuberculosis. Symptoms are absent, there are no abnormal physical signs and roentgenograms rarely bring to light the location of the disease.

In a small percentage of those who in adult life become contaminated for the first time the focus of the disease when located in the pulmonary parenchyma attains sufficient size to cast a shadow on the x-ray film which can be visualized by the naked eye. Such shadows usually become visible during the first three or four months after the

infection has occurred. When these shadows reach their maximum size, they may show the same general appearance over a period of many months, after which they gradually recede. In some cases the shadows remain, revealing evidence of fibrous and calcium deposits, while in others they completely disappear.

The first infection type of tuberculosis as observed in our group of adults has resulted in no significant symptoms or abnormal physical signs throughout the entire course of development. Indeed, the lesions in the majority of our cases would not have been known to exist had it not been for periodic tuberculin testing and the making of roentgenograms of the positive reactors.

In our experience adults in whom the first infection type of tuberculosis develops, even with considerable involvement of the pulmonary parenchyma and regional lymph nodes, do not require treatment in any form.

The prevention of tuberculosis of the first infection type among young adults consists of protecting them against exposure to patients with communicable tuberculosis. For students of nursing and medicine this amounts to a strict technic for dealing with contagious diseases.

Apparently it makes little or no difference at what time of life the first infection with tubercle bacilli occurs, with reference to the evolution of tuberculosis in the human body. When the first infection type of disease occurs in the second and third decades of life it is just as benign as when it occurs in childhood.

Among those persons in whom through exposure to patients with communicable tuberculosis the first infection type of disease develops, whether in infancy, childhood or adult life, including the third decade, a considerable number will subsequently show a reinfection clinical form of tuberculosis.

Tuberculous pleurisy with effusion as it appeared in our group has been regarded as a reinfection form of tuberculosis. It has occurred only among those persons whose tissues were sensitized to tuberculoprotein. In some of our cases the first infection focus in the lung was not located by roentgen examination, while in others it cast shadows definitely visible on the film, and in such cases the shadow usually preceded the appearance of the effusion.

During our period of observation we have seen the complete evolution of tuberculosis and have observed practically every step in its development, from the time before the tissues became sensitized to tuberculoprotein until death occurred from consumption.

There is usually a period of many months or even years between the development of the first infection type of tuberculosis and the appearance of the reinfection type of disease.

In those subjects who became sensitized to tuberculoprotein under our observation and in whom clinical pulmonary tuberculosis later developed, we were unable to see any difference in the intensity of the disease or in the response to treatment from that in a group of young adults in whom reinfection forms of tuberculosis had developed but who were known to have been infected in infancy or childhood.

By roentgen examination alone it is impossible to differentiate between the first infection and the reinfection type of tuberculosis during the earlier periods of development. Neither produces symptoms or abnormal physical signs. Therefore, a long period of observation is entailed. If the lesion proves to be of the first infection type, symptoms and physical signs do not appear, and the shadow gradually recedes. If it is of the reinfection type, symptoms may appear later, abnormal physical signs may be elicited and the shadow on the roentgenogram may increase in size or show evidence of cavity formation or both.

The tuberculin test should be administered to the negative reactors in schools of nursing and medicine at least every six months, since an interval of a year or more between tests materially reduces the value of a positive reaction in differentiating between the first infection and the reinfection type of disease roentgenographically.

The lesions which developed in our group of adults who showed a positive reaction to the tuberculin test when our observations began were similar to the reinfection types of lesions which developed among students after we had seen the benign first infection type of disease develop.

The fact that a roentgenogram of the chest shows no evidence of disease in a subject in the teens or early twenties is no indication that pulmonary tuberculosis will never develop. It is our opinion that this disease may develop in any decade of life from endogenous reinfections or exogenous first infections or reinfections.

The cases of tuberculosis reported in this paper for the most part are from a student body of approximately 12,000. In this student body the number of students enrolled in the schools of nursing and medicine is a relatively small group, yet there is an overwhelming preponderance of lesions in this minor group, indicating to us that the problem of tuberculosis among young adults is most acute among those students who while in the line of duty come in contact with tuberculous patients.

HIGH ALTITUDE DISEASE

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Much has been written on the disturbances produced by high altitudes, but Prof. Monge was the first to establish the existence of definite clinical entities produced by maladaptation to life at a high altitude, studies which were first published in 1928 in a monograph entitled "La enfermedad de los Andes." Prof. Monge has written, at my request, a summary of the disease which justly bears his name—Monge's disease, and it has been my privilege to act as translator.

—E. S. Guzman Barron, Chicago.

A man who is acclimated to the high plateaux of the Andes (from 10,000 to 16,000 feet, 3,000 to 5,000 meters, above sea-level) is, *sensu strictiori,* one who by ancestral or acquired changes has the racial charteristics which allow him to behave physically and mentally like a man living at sea-level. Thus it has been shown by many investigators that dwellers at a high altitude differ from those at sea-level both from an anthropologic and from a biologic point of view. Among the differences have been noted erythremia, an increased viscosity of the blood, a diminished oxygen saturation of the arterial blood, an increased vital capacity and a diminished carbon dioxide tension of the arterial blood.[1]

Acclimation to a high altitude may be congenital or acquired. The first type defines itself. The second type requires a readjustment of the biologic mechanisms for fitness to life at a high altitude. It is interesting in this connection to recall Father Calancha's [2] observations, published in 1639, that the Spanish conquerors who went to the mines of Potosi, Bolivia, at an altitude of 14,000 feet (4,300 meters) had no offspring until fifty-eight years after the city was founded. The mechanisms which enabled the Spaniards to become adapted were established slowly indeed.

It is a matter of common experience that many persons living at high altitudes, whether natives or not, have either lost or failed to acquire the necessary adjustments for a normal life in these regions. The acute form of maladaptation, mountain sickness, has been described

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From the Medical Clinic, the Faculty of Medicine.

1. Monge, M. C.: La enfermedad de los Andes, Lima, Facultad de Medicina de Lima, 1928. Les erithrémies de l'altitude, Paris, Masson & Cie, 1929; Climatophysiologie et climatopathologie des haux plateaux, in Fraité de climatologie biologique et médicale, Paris, Masson & Cie, 1934.

2. de la Calancha, Antonio: Crónica moralizada de la orden de San Augustin, Barcelona, Imp. Pedro Lacaballeria, 1639, vol. 1.

many times, and its symptoms need not be discussed here. Of interest, however, are the bodily disturbances produced by the prolonged effects of a high altitude on those unadapted subjects, clinical entities which my colleagues and I observed among the residents of the Peruvian Andes in the course of our studies of the pathologic conditions due to high altitudes and which have been described under the name Andes diseases.

The clinical picture of high altitude disease may present a variety of forms, the predominance of a particular symptom depending on the degree of damage produced in the different organs and tissues by prolonged anoxemia. It has nevertheless been possible to observe the predominance of two types of this disease: (1) an erythremic type, which we have designated *high altitude erythremia,* on account of the resemblance of the symptoms to those of the Osler-Vaquez erythremia; and (2) an emphysematous type, in which the respiratory symptoms are more important. Also, we have observed numerous patients with cardiac, renal and digestive disorders caused by prolonged anoxemia due to living at a high altitude.

HIGH ALTITUDE ERYTHREMIA

This type of high altitude disease has been the one most frequently observed by us. It may take one of two forms: a mild, *subacute mountain sickness,* or a severe, *chronic mountain sickness.*

Subacute Mountain Sickness.—The symptoms of this form of mountain sickness appear insidiously and are characterized by a slight diminution in mental and physical fitness. The patient complains of general fatigue which bears no relation to the work he performs. It is in these cases that the characteristic erythremic color of the dweller at a high altitude is seen. The patient becomes cyanotic when he makes the least effort. Cephalalgia sometimes appears after a brief mental effort has been made; there is a tendency to sleepiness, which is easily interrupted by a sensation of asphyxia, which disappears after voluntary breathing occurs. More frequently respiration is of the periodic type. There is marked congestion of the mucous membranes (ocular, nasal and oral), and epistaxis, aphonia and ostalgia are marked (the Indian word *macolca* designates this symptom). Digestion is slow, and constipation appears. Loss of weight is generally noted. The patient with the more benign form, if he came originally from sea-level, thinks himself acclimated and goes on with his daily work, to find later that he is unable to keep up the kind of life to which he was accustomed at sea-level. If the disease continues nausea appears, sometimes with vomiting, dizziness and a diminution of the visual acuity, which is

characterized by difficulty of continuous reading and is expressed by the patient as "cloudiness" of vision. Varied paresthesias, such as paracusia, occur. Sometimes these symptoms subside. In some cases the patient goes back to a city at sea-level to consult a physician and finds with surprise that all his symptoms have disappeared. He is sent home by the doctor, who says that the condition is due to nervousness; but once the patient is back at the high altitude the symptoms reappear. This form of the disease permits the patient to live for a long time. The number of red blood cells in such a patient is about 7,000,000 per cubic millimeter. The number of leukocytes is sometimes slightly

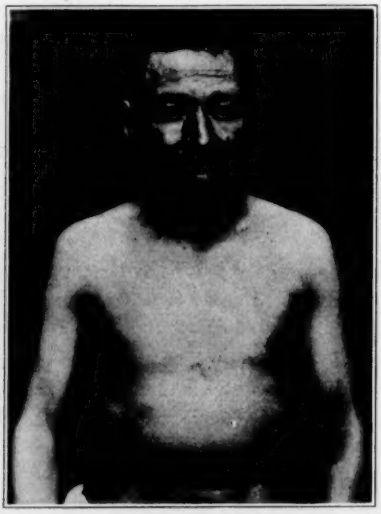

Fig. 1.—A native of Peru with high altitude disease.

increased, and there is a slight increase in the number of monocytes. We have at times observed a few macrophages in the peripheral blood, their presence having no relation to the severity of the disease. The hemoglobin in the blood is increased from 10 to 20 per cent. The p_H of the blood (colorimetric) in the five cases in which it was measured was 7.48. (For twenty-two normal subjects in Oroya, Peru, at 12,200 feet [3,650 meters] we found an average of 7.45.) The basal metabolic rate, studied in collaboration with Hurtado,[3] was found to be normal in seven of ten cases; in the other three it was below normal (—31, —27 and —16, respectively). The disappearance of the disease means

3. Hurtado, A.: Am. J. Phys. Anthropol. **17**:137, 1932.

complete acclimation to life at a high altitude. Otherwise, severe and important symptoms may appear, such as those grouped under the name chronic mountain sickness.

The Severe Form of High Altitude Erythremia, or Chronic Mountain Sickness.—In this form of the disease the resting patient becomes florid and turns purple at the least effort; the erythremic aspect is more striking in natives because of their dark color. In a white patient the skin appears blue. This characteristic color is more noticeable in the face, ears, nose and hands, the dark cyanotic color being more conspicuous when compared with the brownness or whiteness of the body. In cases of severe involvement the scleras are intensely colored by the distended capillaries, the eyes being hidden behind edematous and bluish

Fig. 2.—The characteristic appearance of the hands of a patient with high altitude disease.

eyelids; the face is blue-violet, almost black, resembling that of an asphyxiated person; the nasal and oral mucosae are wine red; epistaxis is frequent; aphonia is usually noted, and the tongue appears larger than normal and full of blood, with prominent papillae. The skin of the body is dry, while the forehead and hands are covered with sweat, even in cold weather. The hands become enlarged and turgid, accompanied with considerable distention of the superficial veins and clubbing of the fingers. The nails become thick, opaque and vertically striated and appear to be inserted like watch glasses. The thorax is large and of an emphysematous type. Walking is slow, the patient being obliged to stop frequently. He resembles an old emphysematous, plethoric patient, walking slowly and heavily. He feels extremely weak, has a marked tendency to sleep and not infrequently is found in a state of

drowsiness, indifferent to what happens outside, with no desires, even to take food. When awakened from this lethargic state he complains of general malaise and a sensation of anguish, spells of dizziness and fainting commonly occurring. Blurring of the vision, nausea and vomiting at the least effort are noted. Sometimes the patient suddenly falls into a coma for two or three hours, to return later to his pitiful condition.

Digestive System.—In general it is an inability to take food rather than anorexia that makes eating difficult, for the discomfort increases considerably after the ingestion of food, and signs of asphyxia frequently come with swallowing. Vomiting is frequent. On occasions there are crises of diarrhea.

Respiratory System.—The patient lives in a state of insufficient hematosis and has incessant dyspnea. The vital capacity diminishes progressively. Aphonia, coughing and frequently bronchitis are present. Sometimes there are also recurring congestive processes in the lungs accompanied with hemoptysis, with or without fever, all of which symptoms rapidly disappear when the patient goes down to sea-level.

Circulatory System.—In the majority of cases cardiac disorders are not found for a long time. We have frequently observed a doubling of the second tone. With the progress of the disease comes cardiac insufficiency. In one case symptoms of angina pectoris appeared after exertion but later disappeared when the patient descended to a low altitude. In this particular case, when the patient tried to keep on walking his vision grew cloudy; he would then become unconscious and fall suddenly. There are no constant alterations in the arterial blood pressure; rarely hypertension occurs. Sometimes a patient is seen who has cardiac insufficiency due to anoxemia without erythremia, the symptoms disappearing as soon as he is brought down from the high altitude. There is generalized dilatation of the blood vessels of the skin and mucosae, which is an exaggeration of a phenomenon normal at high altitudes and which, combined with a plethora of blood, is the cause of numerous disorders. The plethora is responsible also for the considerable loss of blood in case a wound is sustained.

Special Senses.—We have observed a variety of disorders of the sense organs which may be ascribed to dilatation of the capillaries, such as cloudiness of vision; temporary blindness, in which Dammert observed considerable dilatation of the capillaries of the retina, and temporary deafness, in which Raffo observed generalized vasodilatation of the tympanic membrane.

Liver and Spleen.—In only two of seventeen cases in which there was no cardiac insufficiency was the size of the spleen moderately increased. In two cases there was hypertrophy of the liver.

Nervous System.—Patients with this disease complain of a variety of algesias and paresthesias. Some complain of excruciating pain in the lower extremities, with no history of syphilis and a negative Wassermann reaction; others have constant pain in the lumbar region or in the joints, pain of such intensity that they are obliged to remain in bed for several days at a time. This pain may disappear spontaneously. In one case the pain disappeared as the patient descended by train from an altitude of 14,800 feet (4,500 meters) to sea-level in twelve hours. There is sometimes violent cephalalgia. In one instance the cephalalgia subsided after lumbar puncture was performed. Bleeding immediately improves the condition in such cases and is used frequently by the Indians. Paresthesias are varied in type and localization. Some patients complain of unpleasant sensations of heat in the face; others, of violent sensations of cold. One patient said he felt as if warm water were being thrown on his back; another complained of closely localized sensations of pain in the hands and feet. One had the sensation of the loss of one hand; another complained of "bandaged legs." The patients whom we studied while they were at high altitudes unfortunately had had imperfect neurologic examinations, and when they reached sea-level we were unable to find any signs of importance.

Mental Disturbances.—In cases of severe involvement it is possible to find marked disturbances in the behavior and memory of the patients, the entire psychic personality appearing altered. One of our patients, an engineer, had crises of mental confusion during which he would make gross mistakes in arithmetic and drawing, mistakes which he corrected once the crisis was over. As the disease advances the patient becomes apathetic and indifferent to his environment; nothing interests him, and even with the knowledge that descending to sea-level will effect a cure, he does not take the initiative in making the trip. One of our patients who felt ill and tired at a high altitude refused to go down to sea-level when advised to do so. He was taken down while in a coma, which disappeared as soon as he reached sea-level. It should be mentioned that similar observations have been made by Barcroft in his studies with pneumatic chambers.[4]

Blood.—Marked polycythemia is the characteristic feature in these patients, the number of red blood cells being as a rule around 7,000,000, i. e., higher than the average count at those altitudes, which is about 6,000,000. In one case we found a count of 9,060,000 erythrocytes. The number of reticulocytes also is increased. There is slight leukocytosis in most cases, although in one instance we found only 4,000 leukocytes. There is a predominance of monocytes, and in some cases we noted

4. Barcroft, J.: J. Physiol. **42**:63, 1911.

macrophages and cells of the histiocytic type. We were not able to study the platelets. Alterations in the process of clotting are manifest. One patient had bleeding of the gums when he lived at an altitude of 14,800 feet (4,500 meters), but this disappeared as he went down to a level of 14,000 feet (3,700 meters). In another case the patient had convulsive attacks accompanied with purpura and the presence of blood in the cerebrospinal fluid, all of which disappeared when he was brought down to sea-level. Epistaxis is frequent. In general the bilirubin content of the blood is increased (1.28 mg. per hundred milligrams in one case and 1.62 mg. in another). The van den Bergh reaction is of the indirect type. The p_H of the serum, like that of a normal subject living at a high altitude, is slightly more alkaline than when he is at sea-level. In one case of coma the p_H of the serum was found to be 7.35, while after the crisis had passed it went up to 7.45. The alkaline reserve of the plasma is greater than that of a person who is acclimated to a high altitude. When a patient is brought to sea-level no perceptible alteration in the acid-base equilibrium is noted, as the composition of the blood returns to normal quickly. Determinations of the protein content of the blood have not given concordant figures. In one case there was a diminution of about 50 per cent; in other cases normal values were obtained. The concentration of hemoglobin in the blood is considerably increased, in one case reaching 179 per cent (taking 100 as the value found at sea-level). In this particular case 90 per cent of the blood volume was made up of erythrocytes, as determined with the hematocrit. As a consequence of the increased concentration of hemoglobin, the viscosity of the blood is increased. The oxygen saturation of the arterial blood is decreased. Hurtado found in one of our patients a saturation of 57 per cent. Although we have not yet studied systematically the relationship of the oxygen saturation of the arterial blood, the utilization of oxygen and the severity of the symptoms in this disease, we give in table 1 the oxygen utilization (studied in Oroya, Peru) in one adapted subject and two patients. We may say that all these chemical studies were only of a preliminary nature and that well coordinated biochemical studies are of prime necessity in determining the exact nature of the disease.

Basal Metabolism.—While the basal metabolism of normal persons living at a high altitude is normal, according to Hurtado,[3] in ten persons who presented the symptoms of mild erythremia we obtained the following figures: —1, —14, —3, —4, 0, —31, —9, —27, —6, —36 and —12. It seems that in these mild forms of the disease there is a diminution of the basal metabolism, which approaches and reaches normal values with acclimation. In table 2 are given the data obtained by Hurtado for six of our patients who were suffering from severe erythremia. The

difficulty of making studies of the gas exchange in untrained, ignorant persons prompts us to be cautious about our investigations in this subject.

Genito-Urinary System.—The patients frequently complain of sexual frigidity. We have seen patients with albuminuria which disappeared when they were brought to sea-level but which returned as soon as they went back to the high altitude. One patient, who lived at an elevation

TABLE 1.—*Data on the Utilization of Oxygen by the Tissues of Normal and Erythremic (Due to High Altitude) Subjects at a High Altitude*

	Normal Subject		Erythremic Subjects	
	At 150 M.	At 3,700 M.	Severe Erythremia at 3,700 M.	Improved at 150 M.
Hemoglobin, %.....	100.0	117.0	178.0	105.0
Arterial blood				
Oxygen saturation, %.....	96.0	88 0	56.0	81.0
Oxygen tension, mm.....	110.0	65.0	35.0	52.0
Oxygen in blood, vols. %.....	18.5	21.6	32.9	19.4
Venous blood				
Oxygen saturation, %.....	58.0	56	45	54
Oxygen tension, mm.....	37.0	36	31	35
Oxygen utilized, %.....	38.0	32	11	27

TABLE 2.—*Data on the Basal Metabolism Obtained by Hurtado for Patients with Severe Erythremia at an Altitude of Three Thousand, Seven Hundred Meters* *

Age	Height, M.	Weight, Kg.	Surface Area, Sq. M.	Pulse Rate per Min.	Respiration per Min.	Basal Metabolic Rate (Aub-Du Bois), %
60	1.56	51.9	1.50	78	12	+67
47	1.60	56.6	1.59	84	12	+20
31	1.67	75.4	1.85	75	16	+23
56	1.63	73.4	1.80	58	18	+18
29	1.65	59.0	1.65	60	16	+15
33	1.53	57.7	1.56	48	18	+30

* The barometric pressure was 480 mm. of mercury and the temperature from 13 to 18 C. (55.5 to 65 F.).

of 13,000 feet (4,000 meters), came to sea-level complaining of definite symptoms of renal insufficiency; the symptoms subsided and disappeared while he was at sea-level.

Evolution of the Disease.—As a rule, the patients consult a physician only after the illness has been present for some time, for from two to twenty years in about one hundred patients seen by us. Sometimes a patient becomes temporarily well even while staying at a high altitude. As a rule, after a stay at sea-level a patient can return to a high altitude and live there for some time without great discomfort. As time goes on, however, the cure at sea-level is less and less enduring, and asphyxial

disorders may occur as soon as the patient reaches a high altitude, disorders which sometimes end in death. Yet even in cases of severe involvement accompanied with anoxemic coma, a descent to sea-level brings general improvement. If the patient stays at a high altitude death may result from hemorrhage, pulmonary thrombosis, bronchopneumonia or progressive cardiac insufficiency.

We must point out the great similarity between the erythremic type of this disease and the essential erythremia first described by Vaquez, the difference being that erythremia due to a high altitude subsides immediately when the patient descends to sea-level.

EMPHYSEMATOUS TYPE

The emphysematous patient always has a long history of frequent bronchitis and laryngitis. The dominant symptom is dyspnea, which develops after the least effort. Cyanosis occurs rapidly. It is not uncommon to see repeated attacks of congestion of the lungs accompanied with hemoptysis. The thorax is globular, with increased resonance to percussion; the vital capacity is considerably diminished. The fingers are clubbed. The insufficiency of the right side of the heart appears rapidly. The pulmonary ventilation is diminished, and as a consequence the alkaline reserve and the alveolar carbon dioxide content are relatively increased. We may say that the condition resembles that described by the Argentine clinicians as Ayerza's disease.[5] Hurtado, who has studied this type particularly,[6] found a low oxygen saturation in the arterial blood (ranging from 72 and 65 to 55 per cent). In one case he found a high carbon dioxide content in the arterial blood. In those cases in which there is accompanying acidosis, the symptoms disappear slowly, even when the patient is brought to sea-level.

From this condensed description it is seen that the fundamental characteristic of high altitude disease, the characteristic which has made us group it as a nosographic entity, is the fact that all the symptoms subside or disappear as soon as the patient is brought down to sea-level. This feature is undoubtedly due to a common cause, anoxemia. The predominance of any one symptom must be due to the fact that the particular organ involved has suffered the most damage from the prolonged effects of oxygen want.

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5. Escudero, P.: Enfermedad de Ayerza: La enfermedad de Ayerza y los cardiacos negros, in Publicaciones de la Clinica del Profesor P. Escudero, Buenos Aires, El Ateneo, 1925, vol. 1, p. 19.

6. Hurtado, A.: Sobre la patologia de la altura, Lima, Minerva, 1930.

BRITTLE BONES AND BLUE SCLERAS IN FIVE GENERATIONS

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The syndrome of brittle bones and blue sclerotics is one of those comparatively rare yet interesting hereditary clinical entities which stir the imagination and excite the curiosity of clinician and investigator alike. It is our purpose here to report a case, including a family history of five generations, and to review briefly some of the recent literature bearing on the subject.

Key [1] in 1926 and Bell [2] in 1928 presented comprehensive monographs on this subject. The former furnished the first complete pathologic study, while the latter investigated particularly the hereditary phase and through an exhaustive study of all reported cases presented the most accurate known statistics as to the incidence. A review of their work should constitute a starting point for any discussion of this subject. To this summary will be added other recent contributions.

HISTORY

According to Bell,[2] fragility of the bones due to cancer, tuberculosis and syphilis was described by Marcellus Donatus (1588), Fabricius (1609) and Fontanus (1639). Courtial (1705) noted that the bones of aged persons are as fragile as those of persons who have taken large quantities of mercury. A few years later the suggestion was made that osseous fragility may be inherited, but since the various causes of fragility, such as cancer, osteomalacia and rickets, were not well known, little progress toward an understanding of the hereditary feature of the syndrome was made. In 1788, however, Eckman noted hereditary fragility in three generations, and by the middle of the nineteenth century records of some thirty families had been collected

1. Key, J. A.: Brittle Bones and Blue Sclera: Hereditary Hypoplasia of the Mesenchyme, Arch. Surg. **13**:523 (Oct.) 1926.

2. Bell, J.: Blue Sclerotics and Fragility of Bone, in Pearson, K.: Treasury of Human Inheritance, London, Cambridge University Press, 1928, vol. 2, pt. 3, sect. 24.

which showed a hereditary tendency to fracture. However, no mention of blue sclerotics was made in these reports.

In other connections, however, abnormally blue sclerotics had received passing notice, and von Ammon [3] in 1841 demonstrated by means of pathologic dissections that the effect is due to the fact that the choroid coat shines through an abnormally thin sclerotic coat. Credit for the first mention of the association of blue sclerotics and fragile bones goes to Spurway.[4] In 1896 he reported the occurrence of hereditary osseous fragility in four generations and remarked on the "curious bluish tinge of the eye-ball . . . common to many members of this family." Four years later Eddowes [5] wrote his classic paper pointing out the association of osseous fragility and blue sclerotics. He reported on four generations of a family and showed not only that the peculiar syndrome was inherited but that it followed the mendelian law, appearing as a dominant character.

In 1917 Bronson [6] and van der Hoeve and de Kleijn [7] independently brought forth the striking observations that persons with this syndrome tend in the third and fourth decades to become deaf. This deafness was later found to be due to otosclerosis. Thus the triad brittle bones, blue sclerotics and deafness was finally established. Later a fourth feature was to be added, namely, relaxation of the ligaments.

NOMENCLATURE

Great confusion has existed in the past and continues to exist in the contemporary literature with reference to the classification of brittle and soft bones. Such a situation is easily understandable when it is considered that in many instances of abnormality of the bones there is no known etiology, and in some cases there is failure to represent even a recognized syndrome. The following terms are encountered, many of which are synonymous: osteogenesis imperfecta, periosteal dysplasia, mollities ossium, osteomalacia, fetal rickets, fragilitas ossium, osteoporosis and osteopsathyrosis. On the other hand, there is a group of well known diseases which produce a variety of osseous lesions. We

3. von Ammon, F. A.: Klinische Darstellungen der angeborenen Krankheiten und Bildungsfahler des menschlichen Auges, Berlin, G. Reimer, 1841, p. 73.

4. Spurway, J.: Hereditary Tendency to Fracture, Brit. M. J. **2**:845, 1896.

5. Eddowes, A.: Dark Sclerotics and Fragilitas Ossium, Brit. M. J. **2**:222, 1900.

6. Bronson, E.: Fragilitas Ossium, Edinburgh M. J. **18**:240 (April) 1917.

7. van der Hoeve, J., and de Kleijn, A.: Blue Sclera, Fragile Bones and Deafness, Arch. f. Ophth. **95**:81 (Jan.) 1918.

are not concerned here with this group, though it may be pointed out that rickets, scurvy, syphilis, metastatic carcinoma, multiple myeloma, osteogenic tumors, bone cysts and hyperparathyroidism can produce changes which make bones either soft or fragile. Descriptive terms derived from these diseases are frequently applied to osseous lesions. The greatest confusion, however, is seen to lie in the group of idiopathic or developmental osseous changes. Probably the best classification for the different types of idiopathic fragility is a modification of that given by Babcock.[8]

I. Hereditary type
   1. Hereditary hypoplasia of the mesenchyme (brittle bones and blue scleras)

II. Nonhereditary congenital type
   1. Osteogenesis imperfecta congenita
   2. Osteogenesis imperfecta tarda (osteopsathyrosis)
      (1) With white scleras
      (2) With blue scleras

III. Nonhereditary acquired type
   1. Osteosclerosis fragilis generalisata (marble bones, or Albers-Schönberg's disease)

IV. Senile type.
   1. Osteoporosis

Osteogenesis imperfecta was first described by Lobstein[9] in 1833. Many observers now believe that the pathologic process is essentially the same in the two types of osteogenesis imperfecta, the term congenital being reserved for multiple fractures present at birth while the term late refers to fragility developing after the second year of life.

Key[1] separated osteogenesis imperfecta entirely from fragility of the bones in persons having definite antecedents with the condition. The hereditary osseous fragility associated with blue scleras he designated hereditary hypoplasia of the mesenchyme. It is with the latter condition that this paper is primarily concerned.

8. Babcock, W. W.: A Text-Book of Surgery, Philadelphia, W. B. Saunders Company, 1935, p. 203.

9. Lobstein, J. G. C. F. M.: Traité d'anatomie pathologique, Paris, F. G. Levrault, 1833, vol. 2, p. 204.

HEREDITY

With few exceptions the disease is remarkably hereditary. Isolated cases have been recorded, however, such as those reported by Bowcock and Lewis,[10] Goin,[11] Loddoni [12] and Dessoff,[13] in which no hereditary influence could be elicited. Bell [14] pointed out that females are especially liable to the condition, constituting 55 per cent of the patients whose cases have been reported. As is the case in night blindness, dichromatism, hemophilia and hereditary atrophy of the optic nerve, females are the more potent transmitters of this anomaly. Furthermore, the disease as represented by its most typical defect, the blue sclerotics, is a true mendelian dominant character. One would expect that 50 per cent of the offspring of a heterozygotic person with this condition mated with a normal person would have blue sclerotics and brittle bones. This, indeed, has proved to be the case in the many series already studied. With the aforementioned exceptions, one may conclude that each affected person has an affected parent and that the affected person, in turn, will have an equal number of affected and unaffected children. The unaffected children will not have affected descendants. A generation is never skipped, as is occasionally the case with hemophilia ("knight's move" of Bateson). Since the deafness occurs rather late in life, its presence is less often recorded in statistics. But just as blue scleras and fragile bones are a part of the syndrome, so also is otosclerosis, and therefore, though appearing late, it conforms to the hereditary rules just enumerated. Bell [15] has contributed a most complete hereditary study of this syndrome.

Recently, interesting cases with a record of the antecedents have been published by Møller,[16] Stevenson and Cuthbertson,[17] Kersley,[18] Holcomb,[19] Constans,[20] Mucklow,[21] Levent,[22] Hilgenfeldt [23] and others.

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10. Bowcock, H. M., and Lewis, G. T.: Brittle Bones and Blue Sclera: Report of a Case with Glycosuria, Ann. Int. Med. **3**:700 (Jan.) 1930.

11. Goin, L. S.: Idiopathic Osteopsathyrosis, Am. J. Cancer **17**:668 (March) 1933.

12. Loddoni, G.: A Case of Blue Sclera (Osteopsathyrosis), Boll. d'ocul. **11**:65 (Jan.) 1932.

13. Dessoff, J.: Blue Sclerotics, Fragile Bones and Deafness, Arch. Ophth. **12**:60 (July) 1934.

14. Bell, J.: A New Pedigree of Human Inheritance, Ann. Eugenics **4**:41 (April) 1929.

15. Bell.[2, 14]

16. Møller, E.: Family Tree of a Patient with Eddowes' Syndrome, Acta med. Scandinav. **69**:223, 1928.

17. Stevenson, G. H., and Cuthbertson, D. P.: Blue Sclerotics and Associated Defects, Lancet **2**:782 (Oct. 10) 1931.

GENERAL PHYSICAL CHARACTERISTICS

Apart from the specific physical defects already enumerated, it has been repeatedly observed that such persons tend to be undersized. They are short and slender and many times refer to themselves as being "small boned." The normal contours are occasionally altered by the development of bony deformities. The literature carries many illustrations of extreme instances in which the limbs and spine are warped into bizarre shapes as a result of many fractures. In addition to these deformities, frequently there is anomalous cranial ossification tending to produce protuberances in various regions. These may be bitemporal, occipital or frontal. Apert, Bach and Odinet [24] described a patient who showed "a voluminous cranium" and "an osseous brim projecting above the ears." The temporoparietal and sagittal sutures have been reported by Bronson [6] as gaping. Arlabosse [25] also reported a case in which there were cranial deformities. Joachim and Wasch [26] studied three patients exhaustively and noticed in all a prominence of the veins, indicating phlebosclerosis. As far as we are aware, that was the first time such an observation had been made. Apart from the abnormal characteristics noted, however, these persons appeared to enjoy good general health and showed the same intelligence as that of their normal brothers and sisters.

BLUENESS OF THE SCLERAS

The blue sclerotics stand out as the most striking feature. As one looks at an affected person, one is struck by the china-blue color of the sclerotics; and as the majority of these subjects exhibit a rather

18. Kersley, G. D.: Brittle Bones, Blue Sclerae and Deafness, St. Barth. Hosp. J. **38**:236 (Sept.) 1931.

19. Holcomb, D. Y.: Fragile Boned Family: Hereditary Fragilitas Ossium, J. Hered. **22**:105 (April) 1931.

20. Constans, G. M.: Blue Sclera and Brittle Bones, Journal-Lancet **49**:507 (Nov. 15) 1929.

21. Mucklow, S. L.: Osteogenesis Imperfecta Tarda (Idiopathic Fragilitas Ossium): Two Cases, Brit. J. Radiol. **6**:294 (May) 1933.

22. Levent, R.: Lobstein Syndrome Compared with van der Hoeve Syndrome, Gaz. d. hôp. **105**:1901 (Dec. 21) 1932.

23. Hilgenfeldt, O.: Contribution to the Disease Picture of Idiopathic Abnormal Bone Fragility, Deutsche Ztschr. f. Chir. **238**:433, 1933.

24. Apert, E.; Bach, E., and Odinet: Presentation of a Family Affected with Osteopsathyrosis and with Blue Sclerae, Bull. Soc. de pédiat. de Paris **26**:21 (Jan.) 1928.

25. Arlabosse, J.: A Case of Fragilitas Ossium with Head Deformities and Blue Sclerotics, J. de radiol. et d'électrol. **15**:92 (Feb.) 1931.

26. Joachim, H., and Wasch, M. G.: Fragilitas Ossium in Five Generations, Ann. Int. Med. **7**:853 (Jan.) 1934.

delicate or even dainty appearance along with the bluish eyes, they have been said to look doll-like. Most students have agreed with the early conclusions of von Ammon [3] that the blue is imparted by the choroid and is more apparent than usual because the sclera is thin and therefore more transparent. Possibly "thin sclerotic" would be a term preferable to the misnomer "blue sclerotic." To substantiate this theory, Bell [2] pointed out that ophthalmologists who have operated on such eyes and who have examined them with the slit lamp believe that the sclera is thin. However, Bronson [6] and later Patterson, quoted by Oast,[27] found the sclera to be of normal thickness. An increased translucency rather than a decreased thickness has been suggested as a cause. Friedberg [28] more recently has found a decrease in the content of lime salts, which he said he believed accounted for the increased transparency. Levander [29] observed an even darker shade near the iris, indicating various degrees of transparency in the sclera.

Fortunately in these persons there does not appear to be an increased liability for other ocular lesions to be associated with this alteration in the fibrous tunic. Visual defects, refractive errors and variations from the normal ocular tension have not been noted to occur more frequently. One is again struck by the sharp differentiation of tissue, not only quantitative but qualitative, which this disease presents.

DEAFNESS

That deafness occurs in this syndrome was first observed by Adair-Dighton [30] in 1912. But full credit must be given to van der Hoeve and de Kleijn,[7] who, simultaneously with Bronson,[6] in 1917, showed that a hereditary type of deafness is really an integral part of the syndrome. This feature most frequently becomes manifest after the subject is 20 years old and is said to be of the type ascribed to otosclerosis. The deafness in otosclerosis is due to a process resembling osteitis fibrosa, occurring in the otic capsule, which on subsiding heals, with the formation of "scar bone" that causes complete ankylosis of the stapediovestibular articulation, thus precluding the transmission of sound waves to the internal ear. There are few reports in the literature of the pathologic study of the ears in these cases. As with most forms of conduction deafness, however, hearing for all air-conducted sounds,

27. Oast, S. P.: Blue Sclerotics and Brittle Bones: Report of Occurrence in Mother and Child, Arch. Ophth. **57**:254 (May) 1928.

28. Friedberg, C. K.: The Nature and Existence of Abnormal Fragility of Bone, Blue Sclera and Impaired Hearing, Klin. Wchnschr. **10**:830 (May 2) 1931.

29. Levander, G.: A Case of Brittle Bones and Blue Sclera, Acta chir. Scandinav. **63**:301, 1928.

30. Adair-Dighton, C. A.: Four Generations of Blue Sclerotics, Ophthalmoscope **10**:188, 1912.

from the lowest through the highest, is impaired, while bone conduction remains practically normal.

Friedberg [28] pointed out that both nerve and conductive types of deafness occur in patients with this syndrome, and he uses this as a strong argument against hereditary hypoplasia of the mesenchyme. He said he believed the syndrome to be due to a defect in the organ and not to a defect in the primitive germ layer. In the family which we studied there was a history of deafness in fifteen of twenty-seven affected members, or 55 per cent. Aside from the fact that the mother of our patient had the otosclerotic type of deafness, we have no means of knowing which type was present in our family. Van der Hoeve and de Kleijn [7] reported cases in which the petrous portion of the temporal bone was opaque to roentgen rays, and they stated that this fact may be an aid in diagnosis because it shows abnormal calcification of the otic capsule. Kompanejetz [31] has described rather extensively the causes of deafness in this disease. Strange combinations, such as those reported by Lannois and Gaillard,[32] occasionally appear. Their patients were totally deaf sisters, one with and one without blue scleras. The blueness was not noted until adult years, and both patients had associated syphilis, making the relation with this syndrome questionable.

FRACTURES, DEFORMITIES AND SPRAINS

To estimate exactly the degree of fragility of bone is difficult. Normal persons have fractures with a fairly constant degree of trauma. The occurrence, however, of two or more fractures in a person with blue sclerotics in contrast to one or no fractures in another member of the same family who has white sclerotics is taken as an indication of fragility. Levander [29] has pointed out that the metaphysis becomes thinner just before it reaches the epiphysial line. Many observers have noted that fractures frequently occur at this site. In contrast to osteogenesis imperfecta, the fractures are not likely to be present at birth but do occur off and on through childhood until puberty is reached. After puberty the bones are less likely to break, and the subject may begin to look forward to a more peaceful and less hazardous existence. Comminuted and compound fractures are rare, though our own patient presents an example of the latter condition. Nonunion is seldom encountered, for as a rule the fracture heals promptly without deformity and without excessive callus. Deformity is due to malunion, not to softening of the bones, and for this reason should usually be pre-

31. Kompanejetz, S.: Case of Deafness with Blue Sclera and Brittle Bones, Monatschr. f. Ohrenh. **64**:193 (Feb.) 1930.

32. Lannois, M., and Gaillard, R.: Blue Sclera and Total Deafness, Acquired and Incomplete, Ann. d'oto-laryng., February 1933, p. 141.

ventable. It has been repeatedly emphasized that the bones are unusually hard though brittle. Conditions characterized by reabsorption of calcium, on the other hand, may well exhibit softening and its attendant bizarre deformities.

The fibrous structures supporting the joints are frequently loose and relaxed, allowing for an unusual range of motion. Many such persons are "double jointed." It is not surprising, therefore, to encounter many instances of sprains and dislocations. Our patient sustained a dislocation of the hip during a simple fall to the pavement. Sprains are said to be more common than dislocations, though the tendency to either is likely to be a prominent feature in only an occasional family.

The roentgenographic appearance of the bones is characteristic, in that the density of the entire bone is decreased. As a rule the cortex is thin, and there is a wide marrow cavity. In contrast to such a diaphysis, however, the epiphyses show a more nearly normal size. Occasionally an excessive amount of calcification has been noted in the petrous portion of the temporal bone—presumably in the vestibular region.

ETIOLOGY AND PATHOLOGY

Most authorities agree that there is some hereditary defect, but its exact nature has never been determined. Key and others have proposed the theory of hereditary hypoplasia of the mesenchyme, and this seems to be the most satisfactory explanation. However, it has been pointed out that many other tissues of mesenchymal origin are not affected and that abnormalities have been noted also in ectodermal and entodermal tissues.

The etiology has been sought by students of the disease among the endocrine glands, and at one time or another every gland has been suspected. Kraus [33] has discussed this thoroughly. Fonseca [34] has reported two cases in which he said he believed that the condition was associated with a derangement of calcium metabolism and in which parathyroid therapy was followed by improvement. For the most part the blood has shown a normal concentration of calcium and phosphorus. Dessoff [13] has recently made out a case for hyperparathyroidism, and this of all the endocrine disturbances seems the most logical to be considered as a causative factor. He cited from the literature two cases of osteogenesis imperfecta associated with enlargement of the parathyroid glands. But it must be pointed out that osteogenesis imperfecta, as well as other metabolic diseases of bone attributable to hyperpara-

33. Kraus, E. J.: Relation of Brittle Bones and Blue Sclera to the Endocrine System, Virchows Arch. f. path. Anat. **274**:37, 1930

34. Fonseca, A.: The Relation of Parathyroid Function to the Syndrome of Blue Sclerotics, Brasil-med. **44**:448 (April) 1930.

thyroidism, is different from the disease under discussion. Furthermore, with few exceptions, the calcium and phosphorus values for the blood in these cases have been normal.

The pathologic changes in the eyes and ears have already been discussed. Key studied the osseous changes thoroughly and noted especially that there are many wide canals running out through the cortex in all directions and communicating freely. In some of the larger canals collections of fat cells are seen. The bone marrow extends a short distance into the canals, where it is gradually replaced by fat, which is in turn replaced by myxomatous tissue. There is a superabundance of osteoblasts, which accounts for the rapid healing of fractures. The tendons and ligaments are small but are histologically normal.

Brittle teeth have occasionally been noted but are rare. Some members of Stobie's [35] family reported breaking a tooth while biting bread. Tanturri [36] reported not only brittle teeth but brittle hair and nails as well. None of these features had been noted in our own cases.

DIAGNOSIS, PROGNOSIS AND TREATMENT

A diagnosis of this condition is founded on the presence of abnormally blue scleras in a person one or both of whose parents had the same characteristic. The presence of the other stigmas is not essential to a diagnosis. As a practical matter, however, most patients are first seen because of a fracture, and a diagnosis is made when the blueness of the eyes is noted.

The prognosis will vary with the individual case. It can be predicted that the fractures will unite promptly. Deformities may result from malposition of the fragments but not from bending of the bones. The most encouraging feature is that puberty so often brings about a cessation of the bone breaking, and thereafter fractures are much less likely to occur. No method is known which will prevent the onset of deafness—a tragically important fact in a youth. A person with this defect who marries may anticipate that one half of the offspring will be similarly affected.

Treatment has been empirical and will continue to be so until an etiologic basis is found. Endocrine preparations, drugs, vitamins, diet and physical therapy have all been employed. No method of treatment, however, has been shown conclusively to have any curative effect. Exploration of the parathyroid glands has been proposed but appears

35. Stobie, W.: The Association of Blue Sclerotics with Brittle Bones and Progressive Deafness, Quart. J. Med. **17**:274 (April) 1924.

36. Tanturri, V.: New Factors in the Complex of Blue Sclera, Brittle Bones and Deafness, Rev. españ. y am. de laring., otol. y rin. **23**:97, 1932.

to us illogical for this particular entity. Breuer [37] stated the belief that he has seen beneficial results after the administration of strontium lactate and calcium phosphate, $Ca_3(PO_4)_2$, the former stimulating the formation of osteoid tissue on which the latter more readily precipitates. Gorter [38] has discussed the use of thymus extract. A patient with well controlled osteogenesis imperfecta tarda has recently been shown to be improved in a report by Secord, Wilder and Henderson.[39] They administered the new thymus extract of Hanson daily for a period of more than three months and were able to demonstrate roentgenographically an improvement in the density of the bones and some thickening of the cortex.

For the present the physician must insist on scrupulous care against injury for the affected child. Fractures when they do occur are treated along accepted lines, the fact being borne in mind, however, that the bones unite quickly and that the period of immobilization may be reduced. Hein [40] has described in detail methods used in treating an infant who had nine distinct fractures, as noted roentgenographically. Deformities may safely be corrected by osteotomy. The eyes ordinarily require no treatment, while for the otosclerosis, at the present writing, there is little to be done.

REPORT OF A CASE

E. M. C., a white girl aged 10 years, was first admitted to the Union Memorial Hospital on July 3, 1930, having suffered a compound fracture of both bones of the left forearm. Her family history revealed that members of four previous generations on her mother's side had suffered from multiple fractures, had blue sclerotics and in later life had been deaf. The child herself enjoyed good general health. There had been a suspicion of rickets in infancy. A year before her admission to the hospital she fractured a bone in the right forearm, the result, as in this instance, of a minor fall.

The general physical examination revealed no abnormality apart from the injury and from the observation that the child had abnormally blue scleras. There was an irregular laceration 2 cm. long on the dorsal surface of the left forearm, and both bones showed marked deformity. Roentgen films confirmed the diagnosis of a fracture of both bones of the forearm in the middle third with

37. Breuer, J.: Treatment of Osteogenesis Imperfecta, Deutsche med. Wchnschr. **56**:1735 (Oct. 10) 1930.

38. Gorter, E.: The Treatment of Fragility of Bones with Thymus Preparations, Nederl. tijdschr. v. geneesk. **1**:2022 (April 27) 1929.

39. Secord, E. W.; Wilder, R. M., and Henderson, M. S.: Osteogenesis Imperfecta Tarda (Osteopsathyrosis) Treated with Thymus Extract (Hanson), Proc. Staff Meet., Mayo Clin. **11**:1 (Jan. 2) 1936.

40. Hein, B. J.: Osteogenesis Imperfecta with Multiple Fractures at Birth: An Investigation with Special Reference to Heredity and Blue Sclera, J. Bone & Joint Surg. **10**:243 (April) 1928.

the fragments displaced (fig. 1). Open operation with wiring of the fragments was finally required to obtain a satisfactory result. This was carried out on July 8 by Dr. P. G. McLellan, at that time resident surgeon. The wound healed satisfactorily, and subsequent observation showed prompt solid union. The calcium content of the blood was 9.8 mg. per hundred cubic centimeters, and the

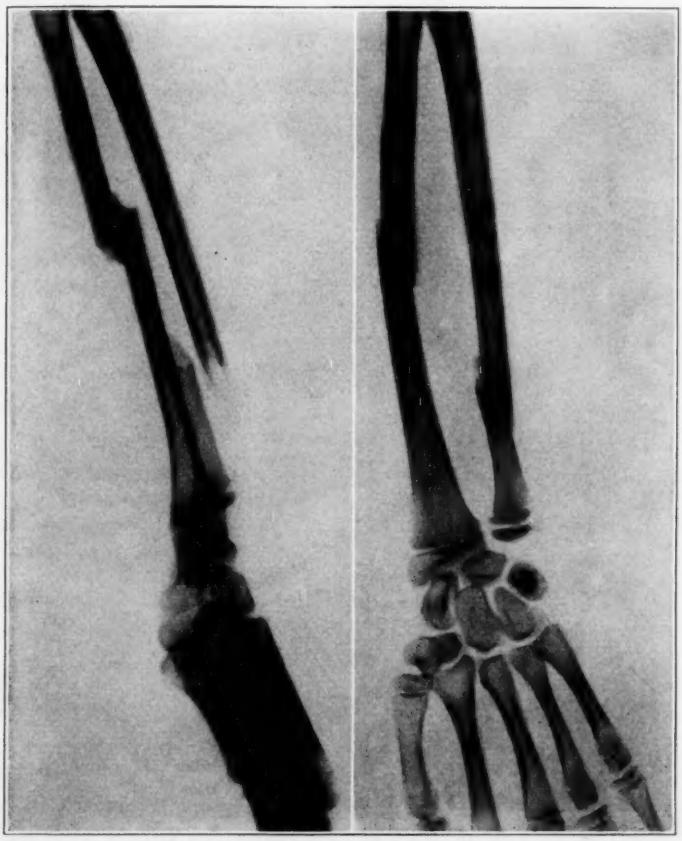

Fig. 1.—Roentgenograms of the left forearm immediately after the fracture was sustained. The small bones, thin cortex and delicate structure are well shown. The patient was 10 years old.

Wassermann reaction of the blood was negative. She was discharged from the hospital on August 20. In the dispensary viosterol was prescribed, and she was seen at intervals of several months.

On Feb. 3, 1932, she was brought again to the hospital, having sustained a compound fracture of the right forearm while roller skating. Roentgen films

revealed a fracture of the lower end of the radius and a separation of the epiphysis of the ulna, fragments of both bones being displaced. With the patient under nitrous oxide anesthesia, the bones were satisfactorily reduced. The calcium content of the blood was 10.02 mg. per hundred cubic centimeters, and the phosphorus content was 4.62 mg., both at the upper limits of normal. The child was discharged on February 8.

Scarcely had the splints been removed when the child fell, on April 15, and again sustained a compound fracture of the right forearm. Reduction was satis-

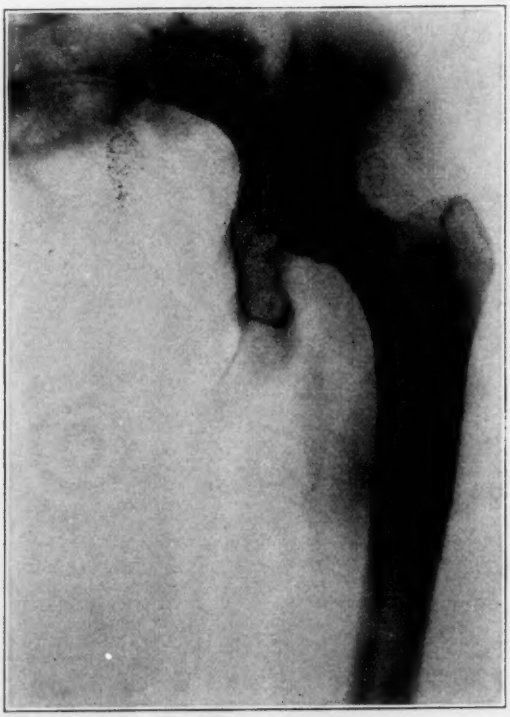

Fig. 2.—Posterior dislocation of the left hip following a simple fall to the pavement.

factory, and she was allowed to return home. This was the fourth time that she had had a fracture of the forearm.

On May 14, only a month later, while jumping rope she fell to the ground and was unable to rise. When seen at the hospital she exhibited the characteristic signs of posterior dislocation of the left hip. A roentgenogram confirmed the diagnosis (fig. 2). With the patient under nitrous oxide and ether anesthesia the dislocation was readily reduced, and a plaster spica was applied. The child was permitted to go home in three days, and the cast was removed in three weeks. She was allowed up on crutches and subsequently walked quite comfortably. On

August 8 she was seen again because of difficulty in walking. Examination revealed increasing relaxation of all the joints. The affected hip was still in proper position, but extended motion was painful. Roentgenograms revealed no abnormality except for some scoliosis and a consequent tilt of the pelvis.

The pain in the hip became worse, and on Feb. 12, 1933, she was admitted to the Mercy Hospital. A diagnosis of arthritis of the hip was made. Manipulation of the joint was carried out, and she was placed in a spica cast, remaining in the hospital until October 27.

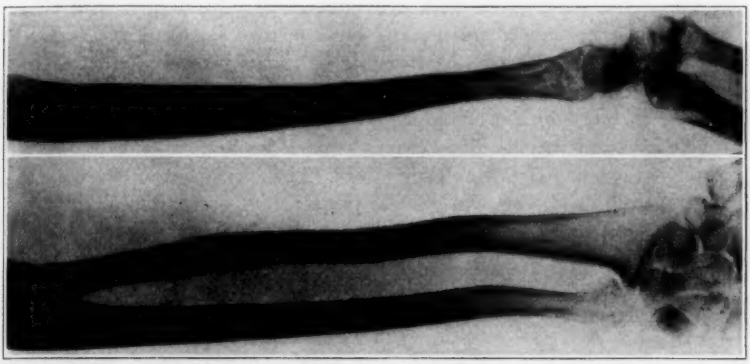

Fig. 3.—Roentgenograms of the right forearm which had been fractured on three different occasions. Union was prompt and solid in each instance. The osseous structure more nearly approached normal as puberty was reached. The patient was 15 years old.

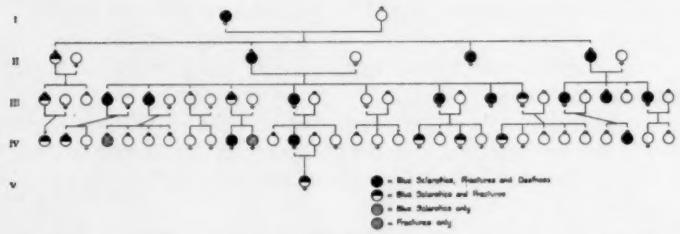

Fig. 4.—The family tree, showing the appearance of characteristic signs in twenty-seven of the fifty-one members.

The hip continued to be painful, however, and walking was awkward, owing to a certain amount of ankylosis. On July 10, 1934, the patient was admitted to the Kernan Hospital for Crippled Children, where subtrochanteric osteotomy was performed by Dr. Albertus Cotton. She left the hospital on September 2. After convalescing from this procedure, the girl has walked without pain and has been quite comfortable, despite the fact that she has complete ankylosis of the left hip. There have been no more injuries. When examined by us in January 1936 she had grown and, though still slight of stature, looked well. The left hip was

ankylosed but gave comparatively little inconvenience, as she appeared to compensate well with the pelvis. We hope that puberty has brought freedom from fractures. Her mother is sensible, however, in refusing the girl's insistent requests for permission to play basketball and to own and use ice skates.

COMMENT

We were fortunate in being able to gain an accurate account of the family, and data were available concerning fifty-one members, including five generations with collaterals. All were traced back to a common ancestor, a woman. Twenty-seven members, approximately half, were affected. Striking is the fact that only one member of the group, a 3 year old child, had blue scleras but had broken no bones. This child is included in the accompanying chart. Sixty per cent of those affected were females. Deafness was manifest in 57 per cent, being more marked in the earlier generations. The incidence of deafness in the last two generations was only 25 per cent, illustrating its occurrence later in life. In no instance did an unaffected member give rise to an affected one. Successive generations revealed lower percentages of affected members. In studying the five persons in direct line, we noticed that all of them had demonstrated the three factors of the disease, with the exception of the 15 year old girl, the patient whose case has been detailed, who was not deaf. It can be predicted with almost certainty that otosclerosis will overtake her in the third or fourth decade of life. The findings in this family are in close agreement with the comprehensive statistics published by Bell.

It has interested us especially that we have been able to follow this child into adolescence and that there has been an apparent cessation of the fracture process, along with an improvement in physique. This observation, made many times before, might well give a lead as to the best therapy.

We believe that it is important that an affected person should be sensibly informed as to the facts of heredity in this disease, so that he may better face the difficult problems of marriage and having offspring.

CONCLUSIONS

This hereditary clinical entity is characterized by four distinct features: blue scleras, fragile bones, a tendency to deafness and marked relaxation of the ligaments.

It is to be distinguished from a large group of nonhereditary conditions associated with soft or brittle bones occurring at all ages and exhibiting many different etiologic factors.

This syndrome is best described as a hereditary hypoplasia of the mesenchyme and follows the mendelian law of inheritance, appearing as a dominant character.

Affected subjects are small. The blue sclerotics are generally attributed to thinness of the sclerotic coat, through which the choroid shines. The deafness is of an otosclerotic type.

The fractures are not likely to be present at birth but occur throughout childhood until puberty is reached. Union is as a rule prompt and complete.

The exact etiology is unknown. The pathologic changes have been carefully studied.

No method of treatment has been shown conclusively to be curative. New approaches along endocrine lines give the greatest promise of being helpful.

One case has been reported in detail. In addition, data have been presented on fifty other members of the same family, showing graphically the occurrence of the primary features of the disease in twenty-six of these.

Dr. Sarah Peyton and Dr. R. R. Norris, of Crisfield, Md., aided materially in obtaining data on the family history, and Dr. Stacy R. Guild, of the Otolaryngological Department of the Johns Hopkins Medical School, cooperated in preparing the section on deafness.

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DIVERTICULUM OF THE PERICARDIUM

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Effusion into the pericardial cavity and inflammation of the pericardium are of frequent occurrence, and the diagnosis is usually made by clinical methods. Congenital absence of the pericardium and cyst of the pericardium have been noted at postmortem examination. A diverticulum of the pericardium, however, is unusual, and a clinical diagnosis has seldom been made. In some cases the diverticulum is probably of congenital origin. Bristowe, Atayas-Maraty, Seidler, Schirmer and Neprjachin have reported cases in which there was a large opening into the sac, with no evidence of a pathologic condition of the pericardium. There is no embryologic or anatomic explanation for the presence of an area of weakness in the pericardium. A traction diverticulum may occur (Luschka), with concomitant cardiac or pericardial disease. In cases of the latter type one may imagine that the pericardium had unusually thin fibers in one area or was weakened by disease and that increased intrapericardial pressure forced an outpocketing through the fibrous layer. In one case the small opening connecting the diverticulum to the pericardium had been closed, possibly by further scarring of the pericardium (Atayas-Maraty). Pericardial diverticula have been described ranging from the size of a pea to that of a pear 12 cm. long. It is interesting that in 52.5 per cent of the cases the diverticulum presented to the right. There is no pathologic explanation for this apparent area of weakness in the pericardium. Histologic examination of the wall of the diverticulum has shown it to be indistinguishable from the pericardium.

The clinical examination may lead one to suspect the presence of an enlarged heart or of a mediastinal tumor. The roentgenologic findings have been carefully studied by Kienböck and Weiss, who have described five cases. In one case the diverticulum was noted at postmortem examination, and that enabled the authors to make a diagnosis in the other four cases roentgenologically. They stated that an abnormal mass, rounded but with somewhat sharp sides, rests against the heart and pulsates. The roentgenographic picture can be confused with that of an aortic aneurysm or a dermoid cyst of the mediastinum. Jansson

From the Department of Medicine of the Lakeside Hospital and the Western Reserve University School of Medicine.

TABLE 1.—*Data on the Location of Diverticulum of the Pericardium*

Position of Diverticulum	Number of Cases	Percentage of Cases
Right side of cardiac shadow	21	52.5
Left side of cardiac shadow	5	12.5
Anterior	5	12.5
Posterior	1	2.5
Lateral	2	5.0
No description	6	15.0

TABLE 2.—*Data for Cases of Diverticulum of the Pericardium*

Author	Date	No. of Cases	Clinical and Pathologic Findings	Cardiac or Pericardial Pathology	Description of Diverticulum
Hart, T.	1837	..	Woman had anasarca; old adhesions in pleural cavity	.....	Diverticulum in anterior portion of mediastinum, opening at point of reflection on aorta; sac contained 3 or 4 oz. of fluid; opening admitted 1 finger
Hird	1848	..	65 year old patient	Vegetation of the mitral valves; surface of heart rough from old effusion of lymph	Pendent cyst connected to right side of pericardium with slitlike opening
Cruveilhier, J.	1849	..	Aged woman; died of rupture of heart into pericardium	.....	Hemispheric pocket in anterior, superior portion of pericardium
Rokitansky, K.	1852	2	No information	.....	Both on lateral part of pericardium
Luschka	1859	3	No information	.....	Largest, size of walnut
Speir, S. F.	1865	..	Woman with palpitation	Palpitation	To left of pleural cavity, large diverticulum; "pericardium absent with arrested development"
Peacock, T. B.	1866	..	No information	.....	Diverticulum 1 inch in diameter with tubular passage 1 inch long; small aperture to pericardial cavity; coats thin and transparent
Bristowe, J. S.	1867	..	Man, aged 47	Aortic and mitral disease confirmed at autopsy	Diverticulum in anterior portion of mediastinum, 1½ inches long; orifice oval, ½ inch long crescentic folds in diverticulum; congenital origin?
Cuffer	1875	..	Diabetic man	.....	Diverticulum over inferior and posterior aspect of pericardium, protruding into mediastinum and connected with pericardial cavity
Baudy	1879	..	Postmortem examination: sclerosis of aortic valves	Aortic sclerosis; heart enlarged; fibrous bands on outer surface	Diverticulum at right inferior surface of pericardium; sac contained 2 oz. of fluid
Cöen, E.	1885	..	Man aged 40; died of nephritis and uremia	Mitral stenosis and insufficiency; aortic insufficiency	Diverticulum, size of hen's egg, at right side of pericardium; circular opening, size of head of pin
Corsini	1890	..	Woman aged 20; died of typhoid and pulmonary complications	....	Cyst between anterior pulmonary artery and vein; started with tube 3 mm. in diameter; two appendixes, 4.5 and 6 cm. long; covered entire wall of heart; wall thin; microscopically wall was like pericardium

TABLE 2.—*Data for Cases of Diverticulum of the Pericardium—Continued*

Author	Date	No. of Cases	Clinical and Pathologic Findings	Cardiac or Pericardial Pathology	Description of Diverticulum
Atayas-Maraty	1895	..	Postmortem examination: diverticulum of congenital origin?	.....	Diverticulum in anterior portion of mediastinum, 11 cm. long, pear-shaped, connected to pericardium by canal 2 cm. by 8 mm.; did not open into pericardial cavity; contained 80 cc. clear lemon yellow fluid; histologic examination: structure comparable to that of pericardium
Piazza-Martinii	1895	..	Man aged 23 died of cardiac failure	Heart bilaterally enlarged	"Cyst" in upper anterior part of pericardium, connected with pericardium, containing same clear fluid
Schrötter, L....	1901	..	Pericarditis following Bright's disease	.....	Diverticulum, size of hen's egg, protruded into right lung, filled with serous fluid
Rohn, A.....	1903	4	(*a*) Woman aged 40	(*a*) Mitral stenosis and insufficiency; pericardial effusion	(*a*) Diverticulum 7 cm. long with 9 mm. circular opening (*b*) Diverticulum to right, 4.5 by 4 cm.; circular opening (*c*) Diverticulum opening to left 4.5 by 2 cm. (*d*) Diverticulum opening to left 1 by 2 cm., with 4 mm. opening posterior
Sehgenti, W....	1921	..	Pericarditis	.....	Diverticulum, 8.5 by 5.5 by 3.5 cm.; wall resembled thin pericardium
Seidler, E.....	1921	..	Woman aged 63; blood pressure 250/170; died of apoplexy	X-ray plate showed mass to right of heart; aneurysm or dilated aorta? probably congenital	Diverticulum, size of hen's egg to right
Schirmer, O....	1923	..	Woman aged 40; generalized tuberculosis and Pott's disease	.....	Two diverticula to right; (1) 2.5 by 2 by 1 cm. with 7 mm. opening; (2) 8 by 9 by 4 mm.; probably congenital in origin
Lauer, W.....	1925	..	Man aged 30; insane; pulmonary tuberculosis	.....	Diverticulum near right auricle, 8 by 6 by 4 cm., containing 5 cc. clear fluid; wall like pericardium but thinner; resembled Meckel's diverticulum
Grabowski, W.	1926	..	Woman aged 50	Syphilitic aortitis and aortic dilatation with resulting aortic insufficiency	Diverticulum at anterior aspect and more to right; 3.8 by 2.2 by 2 cm. with probe-sized opening into pericardium
Neprjachin, G.	1927	..	Man aged 32; pulmonary tuberculosis	Fibrous endocarditis	Diverticulum 1.8 by 1.5 by 6 cm. with pencil-sized opening into pericardium; extended to right, by right auricle; congenital origin?
Kedrovsky, V. V.	1929	..	Woman aged 47 with mitral stenosis	X-ray plate showed heart enlarged to right, with diverticulum seen as triangular shadow	Diverticulum to right 5.5 by 2 cm. with oval opening 3.5 cm. in diameter

TABLE 2.—*Data for Cases of Diverticulum of the Pericardium—Continued*

Author	Date	No. of Cases	Clinical and Pathologic Findings	Cardiac or Pericardial Pathology	Description of Diverticulum
Kienböck, R., and Weiss, K.	1929	3	(*a*) Woman aged 39; followed for 21 years; at 58 years, pulsating tumor to right of pericardium, 13 years after diagnosis of aneurysm	.....	Diverticulum to right; x-ray diagnosis
			(*b*) Man aged 33		Diverticulum to right; x-ray diagnosis
			(*c*) Woman aged 37, followed for 3 years; clinical question of tumor or aneurysm; diverticulum present post mortem; diagnosis in previous two cases then made		
Jansson, G.....	1931	..	Patient followed for 2 years; no change	.....	Diverticulum to right; x-ray diagnosis; rounded shadow to right of pericardium
Wiese, O.....	1931	..	Man aged 20	.....	X-ray diagnosis by Kienböck; diverticulum extended to right
Ypsilanti, H....	1931	..	Man aged 34 with pulmonary tuberculosis; dementia praecox	.....	Diverticulum 9 by 3 by 4 cm. at right lower end of pericardium; indistinguishable from pericardium
Jäderholm, K. G.	1932	2	(*a*) A 54 year old patient	.....	Diverticulum to right, extending into lung field
			(*b*) Woman aged 52 with mitral stenosis; question of interlobar pleurisy; died of cardiac decompensation; proved diverticulum at necropsy		Diverticulum to right, with opening the size of pencil into pericardial cavity near base of right lung close to mediastinum
Kienböck, R., and Weiss, K.	1932	..	.....	.....	Reports cases a, b and c, as in 1929 to right and new case, d, with diverticulum to left; x-ray diagnosis
Kienböck, R., and Weiss, K.	1934	..	(*a*) Further report on first patient, now 66 years of age; diverticulum showed calcification	.....	.....
			(*e*) Man aged 42 with calcified diverticulum		Diverticulum to right; x-ray diagnosis

added another helpful observation by stating that on deep inspiration the shadow becomes long and narrow and with expiration, rounder, shorter and broader.

Beck and Cushing reported nine cases in which there was evidence of increased intrapericardial pressure. The fourth patient in that series was studied in 1931, and roentgenographic examination showed a mass suggestive of an encapsulated pericardial effusion or an aneurysm and definite deposits of calcium in the pericardium. This patient could not be followed and was not seen until July 1935, when he appeared in the dispensary and stated that a nontender mass had appeared on the left side of the chest, close to the "breast bone."

REPORT OF A CASE

A 43 year old Negro laborer had been treated in 1925 for a gumma of the leg. Six years later he reappeared in the outpatient department with the complaint of an aching pain in the right side of the chest which was accentuated by activity and by lying on that side. There were marked distention of the veins of the neck, enlargement of the heart, especially to the right of the sternum, and occasionally extrasystoles. There was no Broadbent sign or pulsus paradoxus. There was no ascites, and the liver was not palpable. The arterial pressure was 136 mm. of mercury systolic and 80 mm. of mercury diastolic. The venous pressure was 22 cm. of physiologic solution of sodium chloride. Roentgenograms showed enlargement of the heart, with indefinite pulsation. A mass (fig. 1) suggestive of an encapsulated pericardial effusion or an aneurysm was present which displaced the heart

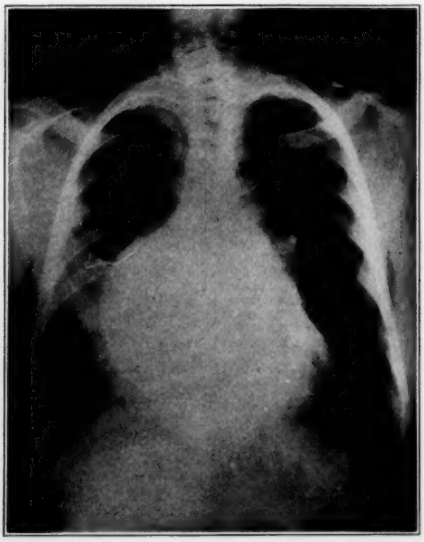

Fig. 1.—A roentgenogram showing widening of the right cardiac outline and calcification in this area.

backward and to the left. The pericardium showed definite deposits of calcium. A dextrocardiogram was slightly irregular, with occasional ventricular premature beats. The voltage was normal.

The patient was next seen in the dispensary in July 1935. He stated that about eighteen months previously he had noted a nontender swelling to the right of the sternum (fig. 2), which had steadily increased in size in spite of repeated aspiration of clear yellow fluid by his physician. There had been increased dyspnea on exertion during the past year. Physical examination revealed a soft, fluctuant, nontender mass, 8 cm. in diameter and 4 cm. in height, between the third and the fifth rib to the right of the sternum. The swelling pulsated with cardiac systole, but there was no thrill. The heart sounds could be well heard over this area. The heart was enlarged to the left, and a systolic murmur was heard at the apex.

The blood pressure was 126 systolic and 100 diastolic in both arms. The remainder of the examination revealed no abnormality. Roentgenographic and fluoroscopic examination showed little change from the plates made four years previously. There was possibly a trifle more calcification in the pericardium. The venous pressure was 400 mm. of water. The 180 cc. of yellowish fluid which was withdrawn showed some involuted acid-fast forms, and inoculation of this fluid into guinea-pigs produced typical acid-fast lesions, causing their death. Inspiration and expiration caused changes in pressure on the manometer which was attached to the tumor, and cardiac systoles also were recorded on the manometer. Fifty cubic centimeters of air was injected into the tumor, and a roentgenogram showed part of the air to be in the pericardial cavity and part beneath the skin (fig. 3). An unsuccessful attempt was made to inject more air in order to outline the pericardium properly.

While the patient was in the hospital auricular flutter developed, but digitalis produced a normal rhythm. The patient felt much better after aspiration of fluid and was discharged, to be followed in the dispensary.

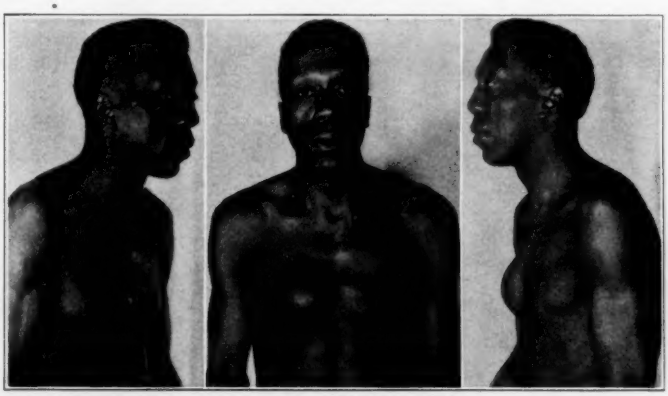

Fig. 2.—Photographs showing the mass to the right of the sternum.

The patient was readmitted to the hospital on Dec. 3, 1935. He stated that he had been well and had had no swelling of the chest or shortness of breath. A week before his readmission to the hospital he had a cold, and the swelling reappeared on the chest. He complained of weakness, nausea and vomiting. There was evidence of retention of food eaten at least six hours previously. Physical examination showed no change in the past six months. Fluoroscopic examination of the stomach showed evidence of an ulcer niche about 1.4 cm. in width and 0.08 cm. deep. The patient was placed on a Sippy diet and atropine, which controlled the gastro-intestinal symptoms. A second fluoroscopic examination made four weeks later showed that the ulcer had disappeared.

The pericardial diverticulum was aspirated twice, and 50 and 45 cc., respectively, of thin, brownish fluid was removed. Smears showed no tubercle bacilli. The intrapericardial pressure fell from 12 cm. of water to 0 at the end of the tap, and the venous pressure dropped from 15 cm. of a 0.25 per cent solution of sodium citrate to 13 cm. There was no change in the blood pressure or in the patient's condition at the end of the procedure.

Air was again injected into the diverticulum and again could be seen in the pericardial cavity. Thickening of the pericardium could be seen over the base of the heart.

Electrocardiograms showed an elevated T wave in the fourth lead. Otherwise there was no abnormality. Removal of fluid from the pericardial diverticulum did not alter the electrocardiographic picture, and the electrical axis did not change.

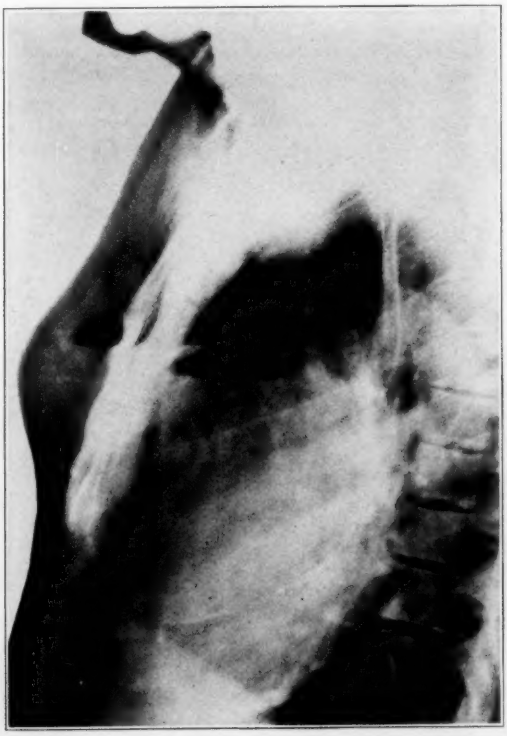

Fig. 3.—Air is present in the subcutaneous mass and in the pericardial cavity. Note the thickness of the pericardium and the calcification.

COMMENT

This case is the first described in which a pericardial diverticulum has presented on the anterior wall of the chest. The diagnosis was confirmed by injecting air into the subcutaneous mass and finding air within the pericardial cavity. The roentgenographic findings were typical of those in the cases described by Kienböck and Weiss and by Jansson. The diagnosis of calcified tuberculous pericarditis was con-

firmed by the demonstration of tubercle bacilli in the pericardial fluid obtained by aspirating the diverticulum and by the death from tuberculosis of guinea-pigs inoculated with the fluid.

SUMMARY

Thirty-nine cases of diverticulum of the pericardium have been described in the literature, and one additional case is reported here.

NOTE.—An additional case of pericardial diverticulum on the right side was described by Ernst, with the typical shadow shown to the right side of the heart in the roentgenogram.

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PATHOGENESIS OF ERYTHEMA NODOSUM

WITH SPECIAL REFERENCE TO TUBERCULOSIS, STREPTOCOCCIC INFECTION AND RHEUMATIC FEVER

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Considerable attention has been directed in recent years to the etiology of erythema nodosum. Various explanations for this cutaneous eruption have been given and include the following: (1) It is a manifestation of tuberculosis; (2) it occurs as part of the symptom complex of rheumatic fever; (3) it has its origin in streptococcic infection; (4) it is a specific infectious disease the etiology of which is not known, and (5) it may occur during the course of various infections, and any one of a number of toxic and bacterial agents may be the cause, including the tubercle bacillus and the hemolytic streptococcus.

While most writers appear to accept the tuberculous concept of erythema nodosum, my colleagues and I have been impressed by the close association which the appearance of this eruption has with streptococcic infections. Because of the apparent confusion in the literature and our own previous observations, the following studies were carried out. My purpose here is to point out that erythema nodosum is a nonspecific inflammatory reaction of the skin due to a variety of agents, including the tubercle bacillus and the streptococcus.

METHODS

In addition to a review of the literature, two methods of approach were followed in this study. First, clinical and experimental studies were carried out on ten patients with erythema nodosum. These included nine females and one male. In an endeavor to elicit any precipitating factor in the patient's illness the following means were employed: A careful history was obtained in each case with particular reference to any recent infection or exposure to tuberculosis; repeated roentgenologic examinations of the lungs were made, and when sputum could be obtained examination was made for the tubercle bacillus; for patients in whom rheumatic fever was suspected, at least one electrocardiogram was taken, and repeated observations were made of the sedimentation rate of the erythrocytes; cultures of material from the nose and throat were studied by the pour plate method for hemolytic streptococci; aerobic cultures were made of venous blood also; teeth

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with clinical or roentgenologic evidence of infection were extracted, and cultures were made of material from the roots and the cavities immediately after extraction. In addition, intradermal tests were performed for each patient with the scarlatinal streptococcus exotoxin, a scarlatinal streptococcus endotoxin (nucleoprotein fraction) and tuberculin in varying amounts. When a hemolytic streptococcus was isolated from either the nose or the throat, a broth filtrate of the organism was prepared and injected intradermally into the patient. Histologic examinations were made of biopsy specimens of spontaneous nodes and of nodes due to the injection of tuberculin and streptococcus nucleoprotein.

The second method of approach was by means of an analysis of the records of one hundred and thirty-three patients treated for erythema nodosum at the Boston City Hospital from 1924 to 1934.

RESULTS OF CLINICAL OBSERVATIONS

Evidence for Tuberculosis.—As far as could be determined, in none of the cases was there a causal relationship between exposure to tuberculosis and the development of erythema nodosum. Repeated roentgenologic examinations of the lungs showed no tuberculous involvement of either the parenchyma or the hilar glands. Mantoux tuberculin tests gave the following results: one positive reaction with 0.001 mg., one with 0.005 mg., three with 0.01 mg. and one with 0.1 mg. In no instance did the injection of tuberculin result in a systemic reaction or the appearance of more nodes. In two cases the tuberculin nodules were slightly tender but pinkish rather than red like the lesions of erythema nodosum. Although the period of observation was less than a year for most of the patients, none showed evidence of tuberculosis.

The following case history illustrates the difficulty encountered in distinguishing between tuberculosis and acute rheumatic fever in a person with erythema nodosum.

R. N., a 16 year old girl, first entered the hospital in June 1934. She had been treated for several years for bronchial asthma. One week before entry she complained of headache and general malaise. Five days later a painful eruption appeared on the anterior surface of the lower part of the legs which was typical of erythema nodosum. Twenty-four hours before entry she had four severe nosebleeds. The cutaneous lesions on the legs gradually disappeared. Soon after she entered the hospital phlyctenular conjunctivitis developed and subsided with local treatment. Because erythema nodosum and phlyctenular conjunctivitis may be associated with tuberculosis, several roentgenograms of the chest were taken, but no lesions were observed. The sedimentation rate was normal three weeks after her entry into the hospital, and she was discharged one week later. She complained of twinges of pain in the joints on walking. She was advised to limit her activities and did so.

Six months after her discharge she reentered the hospital because of chills, fever and migrating polyarthritis. Two weeks later there were signs of fluid at the base of the left lung, and 8 cc. of cloudy, pink fluid, having the characteristics of a transudate, was removed. Guinea-pig inoculation with the fluid showed no evidence of tuberculosis six weeks later. The articular pain and fever subsided

while salicylates were given, and when the latter were omitted because of toxic symptoms, there was an exacerbation of the pain. After the removal of fluid from the left pleural cavity, repeated roentgenologic examinations of the pulmonary fields revealed no abnormality except slight deformity of the heart. Electrocardiograms also were within normal limits. The Mantoux tuberculin and streptococcus nucleoprotein cutaneous tests showed positive results. While the patient was under observation, the character of the heart sounds changed and was thought to be consistent with an early stage of endocarditis. The pulse rate continued to be elevated. The patient was discharged eleven weeks after entry, with the diagnosis of an early stage of rheumatic endocarditis.

The patient immediately entered a sanatorium for patients convalescing from rheumatic fever, where she remained for five and a half months. The sedimentation rate of the erythrocytes was persistently elevated. The patient had intermittent mild attacks of arthritis. There was no essential change in the cardiac signs. She was discharged with the diagnosis of rheumatic fever (?) and potential rheumatic heart disease.

The patient was free from symptoms at home for one month and then complained of pain in the left axillary region. Examination of the chest showed signs consistent with fluid in the left pleural cavity. It had the characteristics of a transudate. Inoculation of guinea-pigs with the fluid has not given evidence of tuberculosis up to the present time. The patient has presented no further evidence of rheumatic heart disease, and the effusion is considered as due to a tuberculous infection until proved otherwise. Subsequently, in guinea-pigs inoculated with the pleural fluid tuberculosis developed. Roentgenograms of the patient's pulmonary fields showed no parenchymatous lesions. Since she had pleurisy with effusion on a tuberculous basis, she was sent to a sanatorium for tuberculous patients.

Evidence for Streptococcus Haemolyticus.—Erythema nodosum was preceded shortly by sore throat in five of the ten patients. One patient had had erythema nodosum three years previously after a severe sore throat. Two patients had sore throats and painful joints. Culture of material from the throat in four cases revealed Str. haemolyticus of the beta type. One-hundredth milligram of the streptococcus nucleoprotein fraction injected intradermally gave marked reactions in eight of the ten patients. The resulting lesions varied in size from 2 to 5 cm., were red and tender and could not be distinguished from the early lesions of erythema nodosum. They appeared from twelve to twenty-four hours after the injection. In two patients a systemic reaction followed the injection, with fever and the appearance of several new lesions on the extremities.

In order to ascertain whether any local immunity to the endotoxin of the streptococcus had developed at the site of the lesion of erythema nodosum, 0.01 mg. of streptococcus nucleoprotein was injected into a node three or four days old. A similar amount was injected into an area of normal skin. The reaction in the node was much less than that in the skin. The same procedure was carried out by injecting

the same amount of nucleoprotein into the lesion produced by a previous injection of nucleoprotein. Again the reaction was much less than that of normal skin.

A filtrate of Str. haemolyticus of the beta type from two patients was prepared by growing the organism isolated from the throat in ordinary broth for twenty-four hours. It was then put through a Berkefeld filter, and saline dilutions were made of the filtrate. One-tenth cubic centimeter of 1:100 and 1:10 dilutions and 0.1 cc. of the undiluted filtrate were injected intradermally into each of the patients. In one case there was no reaction with the diluted filtrates, but there was a slight reaction twenty-four hours later with the undiluted filtrate. The second patient showed an elevated erythematous reaction 2 cm. in diameter with the 1:100 dilution and a reaction 4 or 5 cm. in diameter with the 1:10 dilution and the undiluted filtrate. These lesions were very painful and were similar to the lesions of erythema nodosum on this patient's extremities. This patient was highly sensitive to both the exotoxin and the endotoxin of the streptococcus; and the attack of erythema nodosum was the second one she had had in three years, each one having followed a severe sore throat. Unfortunately, a Dick test was not performed. The remainder of the patients all showed a negative reaction to the Dick test.

It is of interest that the morbidity rate for tuberculous and streptococcic infections is relatively high among the student nurses of the Boston City Hospital. During the past two years there have been only two cases of erythema nodosum among six hundred nurses; these occurred in young women who had severe streptococcic infection of the throat. The following case history is that of one of these nurses.

E. V., a 21 year old student nurse, was first seen in December 1933, when she had a typical attack of tonsillitis. Six months later she entered the hospital because of a herpetic lesion at the site of the exit of the right infra-orbital nerve. Four weeks later she entered the hospital for the third time, because of acute follicular tonsillitis. She complained of pain along the right costal margin. However, repeated roentgenologic studies of the lungs revealed no abnormality. Cultures of material from the throat revealed Str. haemolyticus of the beta type. Although she was asymptomatic in a week, her throat continued to show streptococci for a month. She was treated as a carrier and sent home. One month after her discharge, cultures of material from the throat showed no streptococci with beta hemolysis. She entered the hospital for the fourth time six months later. She had had a sore throat two weeks before. Four days before entry she had acute polyarthritis, and the following day the typical lesions of erythema nodosum appeared on the lower portion of the legs. The patient responded well to salicylates. The sedimentation rate was normal throughout the course of the illness. Electrocardiograms were normal, and roentgenograms of the chest were within normal limits. Culture of material from the throat showed Str. haemolyticus of the beta type. A Dick test showed a negative reaction. Injection of 0.01 mg. of

nucleoprotein intradermally resulted in a typical painful erythematous node at the site of the injection on the forearm, which could not be distinguished from the lesions on the leg. An intradermal injection of 0.05 mg. of tuberculin gave a positive reaction, but this was less severe and painful and pale pink.

The patient made an uneventful recovery, but tonsillectomy was performed six months before this article was written because of repeated attacks of tonsillitis. She has been in good health since then.

Other Etiologic Factors.—There were three females with erythema nodosum who showed no evidence of preceding infection of the upper respiratory tract or of tuberculosis. However, each patient stated that she had an "abscessed tooth" shortly before the eruption developed.

In one case painful nodules appeared shortly after the extraction of a tooth which showed evidence of infection about its roots. In a second patient there was swelling of the left side of the face, due to an infection about a molar tooth, five days before the appearance of erythema nodosum. Cutaneous tests with the streptococcus nucleoprotein and tuberculin showed a marked reaction to the former and a negative reaction to the latter. Roentgenograms of the teeth revealed periapical infection of the right second bicuspid and lower left first molar teeth. These were extracted, and cultures were made of material from the cavities and from the roots of the cystic teeth. The only organism recovered was Staphylococcus albus. In the third patient erythema nodosum developed after the patient had been in the hospital for three and a half weeks. She had entered because of a fractured leg. There were no other patients with erythema nodosum in the hospital at the time. The patient was not placed in isolation, and in no one attending her and in no other patient did erythema nodosum develop. The patient showed marked local and systemic reactions to the intradermal injection of streptococcus nucleoprotein. The tuberculin test gave a negative result.

HISTOLOGIC EXAMINATION OF THE NODULES

A nodule was excised from the lower portion of the leg of each of two patients with erythema nodosum, one having a streptococcic infection of the throat and the other an infection about the root of a tooth. The lesions were four or five days old. The tissues were fixed in Zenker's solution and stained with eosin and methylene blue. At the same time biopsy specimens from lesions in the same patients resulting from the intradermal injection of streptococcus nucleoprotein were fixed and stained in the same manner. These lesions were twenty-four hours old. Microscopic examination of the two types of lesions showed them to be similar histologically. The only distinguishing feature between the two was that the twenty-four hour old artificial node showed evidence of an acute reaction, whereas the reaction of the four day old lesion of erythema nodosum was beginning to subside. Figures 1 and 2 are low power photomicrographs of the twenty-four hour and four day lesions, respectively.

Microscopic examination of the four day lesion of erythema nodosum showed that the epidermis was intact. There was focal infiltration of cells in the reticulum

of the derma which extended into the hypodermis. There was edema of the collagen bundles in the derma. The cellular infiltration in the hypodermis consisted mostly of lymphocytes, with a few polymorphonuclear leukocytes and rare eosinophils. The infiltration was perivascular, with the vessels dilated. The area illustrated in figure 1 was deep in the hypodermis, showing a destruction of collagenous and fibrous tissue, with polymorphonuclear leukocytes predominating. Many of the latter cells had pyknotic nuclei.

Examination of the twenty-four hour node due to the injection of nucleoprotein showed that the epidermis was intact. The focal cellular infiltration was more

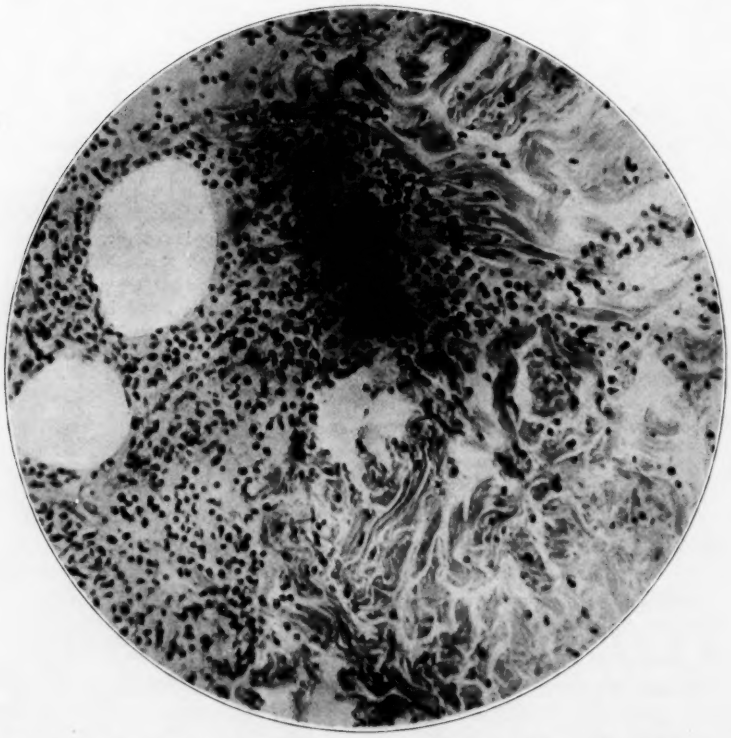

Fig. 1.—Section of a cutaneous lesion from a patient with erythema nodosum twenty-four hours after the intradermal injection of streptococcus nucleoprotein, showing edema of the tissue and round cell infiltration; × 215.

extensive. There was edema of the collagenous tissue. Just under the epidermis was a longitudinal area of cellular infiltration with dilated vessels and also infiltration with young fibroblasts. The cells were mostly lymphocytes, with some polymorphonuclear leukocytes. The areas of focal infiltration were perivascular, with some destruction of adjacent collagenous tissue. Extending down the strands of reticulum into the subcutaneous fat tissue was considerable cellular infiltration.

Figure 2 illustrates a section taken from within the derma, showing edema of collagenous tissue, dilated vessels and cellular infiltration, mostly of the lymphocytic series.

A comparative histologic examination was made of excised lesions due to tuberculin injected intradermally and streptococcus nucleoprotein obtained from an arthritic patient without evidence of either tuberculosis

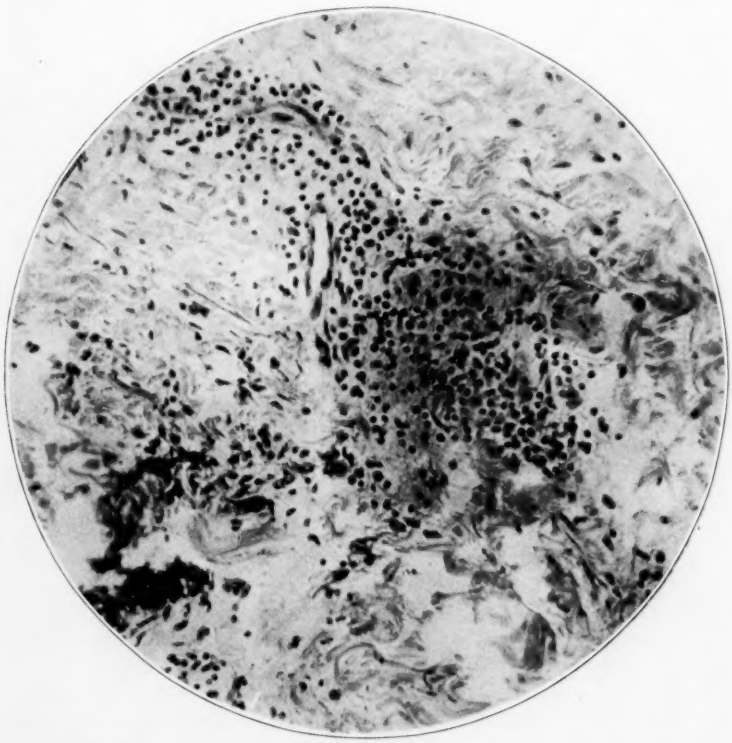

Fig. 2.—Section of a cutaneous lesion of erythema nodosum (four days old) showing edema of the tissue, round cell infiltration and slight necrosis of the tissue; × 215.

or erythema nodosum. The reaction in the tissues was essentially the same as that just described.

Briefly, then, the same type of cellular and tissue reactions was observed in the excised lesions of erythema nodosum as those resulting from the intradermal injections of tuberculin and streptococcus nucleoprotein.

ANALYSIS OF ONE HUNDRED AND THIRTY-THREE CASES OF ERYTHEMA NODOSUM

Age Incidence.—From 1924 to 1934, inclusive, one hundred and thirty-three patients were treated at the Boston City Hospital for erythema nodosum. There were one hundred and eleven females and twenty-two males. Figure 3 shows that the highest incidence of the disease was in females between the ages of 20 and 29 years. Before puberty the sex incidence was about evenly distributed, but after that there was a sharp increase in the number of females. This sex and age distribution is in agreement with reports in the literature.

Seasonal Incidence.—Figure 4 illustrates the seasonal incidence of the cases. The greatest number of cases occurred in the early spring,

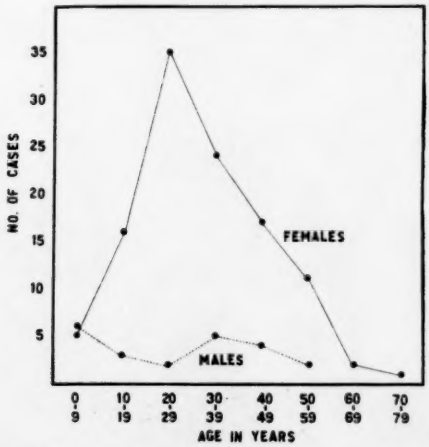

Fig. 3.—Graph showing the age and sex incidence in one hundred and thirty-three cases of erythema nodosum.

the incidence reaching a low level in midsummer and gradually rising early in the fall. Figure 4 shows data for the seasonal incidence of a known streptococcic infection, acute follicular tonsillitis, of which there were ninety-five cases, with Str. haemolyticus of the beta type isolated from the throat in each case. It is seen that the curve of this streptococcic infection closely approximates that of erythema nodosum. Other streptococcic infections, such as scarlet fever and erysipelas, have the same seasonal incidence as tonsillitis. This relationship is not offered as definite proof that erythema nodosum is a manifestation of a streptococcic infection, but it must be considered along with other data presented in this study.

Relationship to Streptococcic Infections and Rheumatic Heart Disease.—Erythema nodosum followed the exposure of several of the patients to streptococcic infection in other members of their respective families. There were forty-one patients (30.8 per cent) who had tonsillitis or acute pharyngitis either before or during the eruption. Fifty-five patients (41.3 per cent) complained of painful joints. Twenty patients (15 per cent) had both a sore throat and painful joints. Because of the latter symptoms and the high incidence of rheumatic fever in New England; that diagnosis was entertained in many of the cases. A series of electrocardiograms was obtained for thirty patients. Twenty-seven revealed no abnormality: there was a prolonged P R interval in two, and one showed evidence of myocardial disease. *Six of the patients with painful joints had definite clinical evidence of rheumatic valvular endocarditis.*

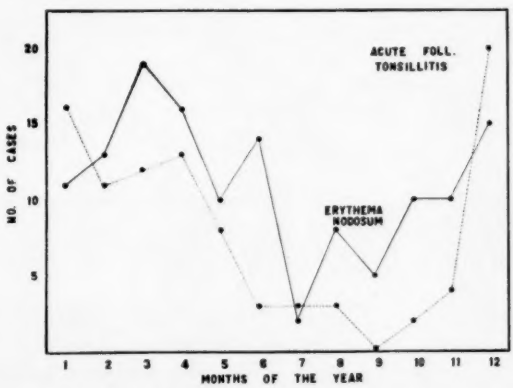

Fig. 4.—Graph showing the seasonal incidence in one hundred and thirty-three cases of erythema nodosum and ninety-five cases of acute follicular tonsillitis.

Considering the state of the heart in more detail, one notes that fifteen patients (11.2 per cent) had rheumatic heart disease. There were five cases of mitral stenosis, nine of mitral stenosis and regurgitation and one of both mitral and aortic stenosis and regurgitation. There was one case each of congenital heart disease and hypertensive heart disease.

One patient entered the hospital with erythema nodosum, Sydenham's chorea and mitral valvulitis. Another patient had been sent to a sanatorium because tuberculosis was suspected. Two months later she entered the Boston City Hospital with erythema nodosum and early rheumatic mitral valvulitis. There was no evidence of tuberculosis.

Relationship to Tuberculosis.—In only two instances was it recorded that erythema nodosum followed exposure to tuberculosis. One patient had been married for nine months to a man with advanced tuberculosis. She had an abortion three months after marriage. No clinical or laboratory evidence could be found for tuberculosis. A second woman had been exposed to a sister with tuberculosis. One examination of the sputum revealed tubercle bacilli, but eleven successive examinations, including a study of two concentrates, gave negative results. Roentgenologic examination showed patchy density at the base of the left lung.

Intradermal tuberculin tests were made in only eleven cases. In four there was a positive reaction and in seven a negative reaction.

Roentgenologic examination of the lungs was carried out in forty-eight cases, and the findings are summarized as follows:

	Cases
Lungs within normal limits	30
Cloudy patch at base of left lung	2
Bronchitic thickening	3
Congestive cardiac changes	3
Enlargement of hilar lymph nodes	3
Old calcified tuberculosis of lungs	2
Abscess in upper lobe of right lung	1
Bronchiectasis	1
Slight clouding of apex of left lung, "not enough for tuberculosis"	1
Fine infiltration in the left side of chest (bronchopneumonia)	1
Enlargement of thymus	1

Before drawing any final conclusions as to the relationship between tuberculosis and erythema nodosum in this series of cases, it is desirable to consider the follow-up study. This study was accomplished in part, as several of the patients had a recurrent attack and returned to the hospital for treatment. A check-up of the remainder of the patients was impossible for there were no available records of their present addresses.

Recurrent Attacks of Erythema Nodosum.—There were eleven patients (8.3 per cent) who had had previous attacks of erythema nodosum from four weeks to fifteen years previously. Roentgenologic studies revealed that only one of these patients showed any changes in the lungs (mottling at the apex of the left lung but "not enough for tuberculosis"). The sputum showed no acid-fast bacilli at several examinations. Two of the patients had a double mitral lesion on a rheumatic basis, one having had erythema nodosum with articular pains seven years previously. At that time there was no evidence of endocarditis. Four of the patients had had preceding infection of the upper respiratory tract, and one had had otitis media which required drainage.

Other Etiologic Factors.—In two cases erythema nodosum developed during convalescence from measles. In three other cases there were cutaneous lesions in association with dental abscesses which required extraction of teeth. Of considerable interest was a man who had gonococcic septicemia and erythema nodosum and who finally made a complete recovery.[1]

It appears, then, from our observations that streptococcic infections play a more important rôle in the etiology of erythema nodosum than tuberculosis. Other workers have not found this same association, and they have emphasized repeatedly that erythema nodosum is a manifestation of tuberculosis. In order to correlate our findings with those of others, the literature on the subject has been reviewed.

Since the tuberculous origin of erythema nodosum is the theory having the most numerous adherents, it will be discussed first. Acceptance of this theory is based on the following observations:

1. The tubercle bacillus has been observed microscopically in the excised lesions of erythema nodosum, and injection of these nodules into animals has caused tuberculosis.[2] An acid-fast bacillus has been isolated from the venous blood of patients with erythema nodosum.[3]

2. Definite clinical evidence of tuberculosis has been demonstrated in patients with erythema nodosum. This has been observed especially in children by Ernberg [4] and Wallgren [5] in Sweden and by Dickey [6] and Hess and Berman [7] in this country. In Copenhagen erythema nodosum was found to occur almost as frequently as pleurisy in persons

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1. This case was reported in detail by Drs. Henry J. Bakst, J. A. Foley and M. E. Lamb (Gonorrheal Septicemia and Erythema Nodosum, Ann. Int. Med. **9**:790, 1935).

2. (*a*) Landouzy, L.: Érythème noueux et septicémies à bacilles de Koch, Bull. Acad. de méd., Paris **70**:400, 1913. (*b*) Arena, A. A.: Existence du Myobacterium tuberculosis dans les nodules de l'érythème noueux, Compt. rend. Soc. de biol. **115**:340, 1934. (*c*) Gutman, R. A.: Un cas de érythème noueux avec présence de bacilles de Koch dans le sang circulant, Paris méd. **21**:416, 1917.

3. (*a*) Brian, O.: Untersuchungen über die Aetiologie des Erythema nodosum, Deutsches Arch. f. klin. Med. **104**:272, 1911. (*b*) Hildebrandt, W.: Zur Aetiologie des Erythema nodosum, München. med. Wchnschr. **54**:310, 1907.

4. Ernberg, H.: Erythema nodosum and Tuberculosis, Am. J. Dis. Child. **46**:1297 (Dec.) 1933; Erythema Nodosum, Nord. med. tidskr. **4**:230, 1932.

5. Wallgren, A.: Paratuberkulöse Krankheitserscheinungen, in Engel, S., and von Pirquet, C.: Handbuch der Kindertuberkulose, Leipzig, Georg Thieme, 1930, vol. 1, p. 809; Tubercle Bacilli in Children with Erythema Nodosum: Demonstration by Gastric Lavage, Am. J. Dis. Child. **41**:816 (April) 1931.

6. Dickey, L. B.: Erythema Nodosum and Tuberculosis in Children, Am. Rev. Tuberc. **26**:614, 1932.

7. Hess, J. H., and Berman, S. L.: Erythema Nodosum in Childhood, M. Clin. North America **12**:49, 1928.

who were in contact with patients with pulmonary tuberculosis.[8] Symes [9] has observed that in persons with erythema nodosum an acute and fatal form of tuberculosis is peculiarly liable to develop within six months. Tuberculous meningitis not infrequently follows an attack of erythema nodosum.[10]

3. Careful follow-up studies over a period of years have shown that in an unusually high percentage of patients with erythema nodosum tuberculosis subsequently develops. This is especially emphasized by Scandinavian workers.[11]

4. In several instances erythema nodosum has appeared in epidemic form in families and among school children after exposure to infectious pulmonary tuberculosis.[12]

5. It has been observed that a high percentage of patients with erythema nodosum show a negative reaction to tuberculin [13] before the eruption but that the reaction often becomes positive during or shortly after the appearance of the cutaneous lesion. A positive reaction to the tuberculin test in children with erythema nodosum has been considered significant. Chaufford and Troisier [14] injected tuberculin intradermally

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8. Holmes, E. M.: Some Aspect of Dermatological Work in Denmark, Brit. J. Dermat. **46**:84, 1934.

9. Symes, J. O.: Significance of Erythema Nodosum, Brit. J. Dermat. **44**: 181, 1932.

10. Foerster, O. H.: The Association of Erythema Nodosum and Tuberculosis, J. A. M. A. **63**:1266 (Oct. 10) 1914. Stokes, J. H.: Erythema Nodosum and Tuberculosis: Report of a Case Terminating in Tuberculous Meningitis, with Necropsy, Arch. Dermat. & Syph. **3**:29 (Jan.) 1921. Meara, F. S., and Goodridge, M.: The Relationship Between Erythema Nodosum and Tuberculosis, with the Report of a Case, Am. J. M. Sc. **143**:393, 1912. Howe, J. Duncan: Erythema Nodosum and Tuberculous Meningitis, Brit. M. J. **2**:864, 1921.

11. (*a*) Giertsen, C.: Ninety-Three Cases of Erythema Nodosum, Acta med. Scandinav. **82**:87, 1934. (*b*) Ustvedt, H. J., and Johannessen, A. S.: Érythème noueux tuberculose ultérieure, ibid. **80**:262, 1933. (*c*) Engelsgaard, H. d'U. A., cited in Erythema Nodosum and Tuberculosis, Lancet **1**:597, 1931. (*d*) Mogensen, E.: Reinvestigations in Erythema Nodosum, Acta med. Scandinav. **80**:480, 1933. (*e*) Forman, L., and Whitwell, G. P. B.: Preliminary Observations on Erythema Nodosum, Guy's Hosp. Rep. **84**:213, 1934. Arena.[2b]

12. Landau, A.: Multiple Cases of Erythema Nodosum in a Class of School Children, Arch. Dis. Childhood **7**:77, 1932. Rotnes, P. L.: Eine Familien-Endemie von Erythema nodosum, Dermat. Ztschr. **67**:259, 1933. Brian.[3a]

13. Gamstedt, E.: Ueber die Tuberkulinempfindlichkeit bei Erythema nodosum vor der Eruption, Monatschr. f. Kinderh. **59**:111, 1933. Laurinsich, A.: Eritema nodoso e tubercolosi, Pediatria **40**:1309, 1932. Heimbeck, J., quoted from Giertsen.[11a]

14. Chaufford, A., and Troisier, J.: Érythème noueux expérimentale par injection intradermique de tuberculine, Bull. et mém. Soc. méd. d. hôp. de Paris **27**:7, 1909.

into a patient with erythema nodosum, and nodules developed which could not be differentiated from the spontaneous nodules.

Ernberg [15] has stated that the histologic appearance of an excised nodule of erythema nodosum is the same as that of the nodule produced by injection of tuberculin into a patient who does not have erythema nodosum. He was able to produce an exacerbation of erythema nodosum in patients by the injection of tuberculin.

6. The blood picture of patients with erythema nodosum shows slight neutrophilic and eosinophilic leukocytosis and monocytosis, which Hoyer [16] claimed resembles an anaphylactic reaction, possibly to proteins of the tubercle bacillus. Móritz and Dóra,[17] studying the local blood picture of the lesions of erythema nodosum and of nodules due to the injection of tuberculin, found a preponderance of lymphocytes in both and concluded that the former lesion is due to an allergic reaction on a tuberculous basis.

7. Phlyctenular conjunctivitis is associated with tuberculosis, and Nobécourt and Ducas [18] and Forman and Whitwell [11e] have emphasized the same association in erythema nodosum.

There is little doubt, then, that erythema nodosum may be a manifestation of tuberculosis. The association appears to be more common in children than in adults. Perhaps the reason we have observed a more frequent association with the streptococcus is that most of our patients have been adults. We have observed the same histologic appearance in the nodule resulting from injections of streptococcus nucleoprotein and tuberculin as in the nodule of erythema nodosum. Even if erythema nodosum is caused by the local activity of the tubercle bacilli, it would be unusual to find the organisms in excised nodules, since Rist and Rolland [19] have shown that if tubercle bacilli are injected intradermally into tuberculous guinea-pigs and the site of the injection is excised in twenty-four hours, it is difficult to find the organisms, as they are quickly destroyed by lysis.

A study of the problem of erythema nodosum similar to ours has been made by Collis [20] in London. He gave cutaneous tests with the

15. Ernberg, H.: Erythema nodosum: Natur und Bedeutung, Jahrb. f. Kinderh. **95**:1, 1921.

16. Hoyer, W. A.: Untersuchungen über das Blutbild bei Erythema nodosum mit Hinblick auf die Aetiologie, Acta med. Scandinav. **57**:587, 1923.

17. Móritz, D. U., and Dóra, A.: Das lokale Blutbild bei Erythema nodosum, Arch. f. Kinderh. **104**:65, 1935.

18. Nobécourt, P., and Ducas, P.: Érythème noueux et conjonctivite phlycténulaire, Presse méd. **42**:1241, 1934.

19. Rist, E., and Rolland, J.: Étude sur la réinfection tuberculeuse, Ann. de méd. **2**:13, 1914.

20. Collis, W. R. F.: A New Conception of the Aetiology of Erythema Nodosum, Quart. J. Med. **1**:141, 1932.

nucleoprotein endotoxic fraction of Str. haemolyticus, tuberculin and the toxin of the scarlatinal streptococcus. In this manner he found that some patients reacted to the streptococcus product and not to tuberculin, and the reverse was true in another group. He concluded that erythema nodosum is a type of hyperreactive response of the tissues to different bacterial allergens and that the allergens responsible for erythema nodosum in London are commonly tuberculin and hemolytic streptococcus endotoxin. However, more recently, Collis [21] has stated that the streptococcic "types" of erythema nodosum are rare and that in the majority of cases in children the condition is tuberculous.

Pilot [22] has observed erythema nodosum as a sequela of streptococcic sore throat. He also isolated the organism and produced typical nodules in these patients by the intradermal injection of streptococcus filtrates. Pilot and Davis [23] have seen erythema nodosum occur in patients with septic sore throat due to Streptococcus epidemicus. Goldstein,[24] Stone [25] and Shepheard [26] have called attention to erythema nodosum in subjects with streptococcic sore throat. Gaub [27] stated that he had obtained the streptococcus from the blood stream of patients with erythema nodosum. Traut [28] has described a patient who showed unusual sensitivity to the streptococcus and who had repeated attacks of Henoch's purpura and erythema nodosum.

Coglievina [29] and Móritz [30] stated the opinion that erythema nodosum may be a complication of scarlet fever, while Slot [31] claimed to have obtained good results with scarlatina serum in the treatment of erythema nodosum.

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21. Collis, W. R. F.: Erythema Nodosum, Lancet **2**:732, 1934.

22. Pilot, I.: Focal Infection and Erythema Nodosum, J. A. M. A. **101**:2145 (Dec. 30) 1933.

23. Pilot, I., and Davis, D. J.: Sporadic Septic Sore Throat, J. A. M. A. **97**:1691 (Dec. 5) 1931.

24. Goldstein, H. I.: Erythema Multiforme and Erythema Nodosum with Streptococcic Sore Throat, M. J. & Rec. **134**:266, 1931.

25. Stone, W. R.: Erythema Nodosum Associated with Streptococcic Faucitis, New York M. J. **118**:673, 1923.

26. Shepheard, E.: Septic Sore Throat Complicated by Erythema Nodosum, Brit. M. J. **1**:902, 1926.

27. Gaub, W. H.: Erythema Nodosum, J. A. M. A. **100**:601 (Feb. 25) 1933.

28. Traut, E. F.: Hypersensitivity in Rheumatic Disease, M. Clin. North America **18**:1237, 1935.

29. Coglievina, B.: Aetiologie des Erythema nodosum, Wien. klin. Wchnschr. **37**:413, 1924.

30. Móritz, D. V.: Erythema nodosum und Scharlach, Arch. f. Kinderh. **103**: 227, 1934.

31. Slot, G.: Erythema Nodosum Treated with Antistreptococcal Serum, Lancet **2**:600, 1934.

Some physicians believe that erythema nodosum is a link in the rheumatic syndrome. Mackenzie [32] was one of the first to point this out. More recently, Holmes,[33] Markson [34] and Claman [35] have observed endocarditis developing in patients with erythema nodosum.

Of less importance is the theory that erythema nodosum is a specific infectious disease the etiologic agent of which is unknown. Evidence in favor of this is that the disease has a definite age and seasonal incidence, it is known to occur in epidemics and the clinical course is one of an orderly sequence of events.[36] Goldberg-Curth [37] stated as her belief that there is a true idiopathic and a symptomatic form of erythema nodosum. She said that it may develop in the course of nearly every infectious disease and as a cutaneous reaction to toxic substances. Fornara [38] stated that he did not think it necessary to have cutaneous lesions in the course of the disease, this being the exception rather than the rule. To explain the relationship to tuberculosis, he stated that cutaneous lesions appear in persons who are hyperallergic—and this is true of tuberculous persons.

Besides the tubercle bacillus, other organisms have been cultured from the lesions of erythema nodosum. Rosenow [39] obtained an organism from several patients which he described as a diphtheroid bacillus closely resembling the streptococcus group. Moon and Strauss [40] have isolated an organism varying greatly in morphology which they have named Corynebacterium cutis-nodosae.

It is our belief that evidence is in favor of the theory that erythema nodosum is the result of a nonspecific reaction to a variety of infectious

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32. Mackenzie, S.: On Erythema Nodosum, Especially Dealing with Its Connection with Rheumatism, Tr. Clin. Soc. London **19**:215, 1886.

33. Holmes, A. H.: Erythema Nodosum, Lancet **2**:784, 1934.

34. Markson, A.: Antistreptococcal Serum for "Rheumatic" Affections, Brit. M. J. **1**:129, 1935.

35. Claman, I. A.: Erythema Nodosum: A Link in a Rheumatic Syndrome, Am. J. Dis. Child. **48**:1448 (Dec.) 1934.

36. Symes, J. O.: Erythema Nodosum: An Acute Specific Fever, Brit. M. J. **2**:741, 1921. Comby, J.: Érythème noueux chez les enfants, Arch. de méd. d'enf. **26**:329, 1923. Woringer, P.: Érythème noueux familial, J. de méd. de Paris **42**:241, 1923. Lendon, A. A.: Nodal Fever, London, Baillière, Tindall & Cox, 1905.

37. Goldberg-Curth, A.: Zur Pathogenese des Erythema nodosum, Monatschr. f. Kinderh. **61**:249, 1935.

38. Fornara, P.: Le problème de l'érythème noueux, Rev. franç. de pédiat. **6**:723, 1930.

39. Rosenow, E. C.: The Etiology and Experimental Production of Erythema Nodosum, J. Infect. Dis. **16**:367, 1915.

40. Moon, V. H., and Strauss, A.: Erythema Nodosum; Character and Etiology, Arch. Dermat. & Syph. **26**:78 (July) 1932.

or toxic agents. Such a point of view has been expressed by Blumer [41] and Josephsen.[41a]

Pilot [22] and others [42] have observed the development of erythema nodosum in patients with lymphogranuloma venereum. Pilot produced a typical lesion of erythema nodosum in a patient with lymphogranuloma venereum by the intradermal injection of the Frei antigen.

Elwell [43] presented an instructive case in which several attacks of erythema nodosum and an axillary abscess were related to infection about the teeth.

Erythema nodosum has been reported as occurring in the course of chronic meningococcic septicemia,[44] in syphilis,[45] after influenza [46] and in association with ulcerative colitis.[47]

The drugs that have been implicated as the cause of erythema nodosum are bromides [48] and potassium iodide.[49]

CONCLUSIONS

Since a variety of toxic agents may be the cause of erythema nodosum, careful clinical observations are necessary in every case to determine the precipitating factor. It may be a manifestation of tuber-

41. Blumer, G.: The Febrile Types of Erythema Multiforme and Erythema Nodosum, New England J. Med. **195**:515, 1926.

41a. Josephsen, G.: Erythema Nodosum, Ugesk. f. læger **95**:423, 1933.

42. Amtman, L., and Pilot, I.: Lymphogranuloma Inguinale, Arch. Dermat. & Syph. **26**:868 (Nov.) 1932. Hellerström, S.: A Contribution to the Knowledge of Lymphogranuloma Inguinale, Acta dermat-venereol. (supp.) **1**:5, 1929.

43. Elwell, L. B.: Erythema Nodosum and Focal Infection, Brit. M. J. **1**:974, 1935.

44. Montgomery, L. C.: Chronic Meningococcal Septicemia, Canad. M. A. J. **20**:266, 1929. Master, A. M.: Meningococcemia with Endocarditis, J. A. M. A. **96**:164 (Jan. 17) 1931. Netter, A.: Fièvre intermittente par septicémie méningococcique, Bull. et mém. Soc. méd. d. hôp. de Paris **41**:1018, 1917. Morgan, J. H.: Chronic Meningococcus Septicemia, Bull. Johns Hopkins Hosp. **32**:245, 1921.

45. Leviseur, F. J.: Erythema Nodosum Syphiliticum (Mauriac's Disease), J. Cutan. Dis. **29**:579, 1911. Stillians, A. W., and Senear, F. E.: Erythema Nodosum Syphiliticum, Arch. Dermat. & Syph. **1**:607 (May) 1920. Fischl, F.: Erythema nodosum lueticum; Spirochätenbefund und Histologie, Arch. f. Dermat. u. Syph. **129**:361, 1921.

46. Boganovitch, V.: Five Cases of Post-Influenzal Erythema Nodosum, Arch. Dis. Childhood **5**:56, 1930.

47. Brooke, P. A.: Erythema Nodosum-Like Lesions in Chronic Ulcerative Colitis, New England J. Med. **209**:233, 1933. Rankin, F. W.; Bargen, J. A., and Buie, L. A.: The Colon, Rectum and Anus, Philadelphia, W. B. Saunders Company, 1932, p. 238.

48. Weber, F. P.: Erythema Nodosum with Tuberculous Bacillaemia and Meningitis, Brit. J. Child. Dis. **21**:119, 1924.

49. Perrin, L.: Un cas d'érythème noueux dû à l'iodure de potassium, Marseille-méd. **29**:567, 1892.

culosis. It appears from the literature that this association is more common in children. Streptococcic infection, especially of the upper respiratory tract in adults, often precedes the eruption. In our experience this association has been more common than that of tuberculosis and erythema nodosum. It may occur in patients with evidence of acute rheumatic fever. Erythema nodosum sometimes appears to be related to infection about the roots of teeth. There also appears to be a group of cases in which the causative agent cannot be elicited. All persons with erythema nodosum should be followed carefully after recovery for evidence of tuberculosis, endocarditis or a focus of infection, for instance, around the roots of the teeth.

SUMMARY

Ten patients with erythema nodosum were critically studied.

No evidence of tuberculosis was present, except in one patient.

The following data indicate a causal relationship between Str. haemolyticus and erythema nodosum: In five of the ten patients erythema nodosum was preceded by a sore throat, and cultures in four cases revealed Str. haemolyticus of the beta type; intradermal injection of a streptococcus endotoxin (nucleoprotein) produced nodules similar to the lesions of erythema nodosum in eight of the ten patients; excised streptococcic nodules and the lesions of erythema nodosum revealed the same histologic appearance; similar lesions were produced by the injection of broth filtrates of streptococci isolated from two of the patients. The same picture has been produced by the injection of tuberculin.

An analysis of the records of one hundred and thirty-three patients treated for erythema nodosum at the Boston City Hospital from 1924 to 1934 revealed a similar causal relationship to streptococcic infections and, in addition, to rheumatic fever.

A general review of the literature is presented.

Erythema nodosum appears to be a nonspecific inflammatory reaction of the skin to a variety of bacterial, toxic and chemical agents.

ESSENTIAL THROMBOPHILIA

REPORT OF FIVE CASES

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There are three well defined occlusive diseases of the arteries: thrombo-angiitis obliterans, thrombo-arteriosclerosis obliterans and occlusion due to embolism.[1] In our experience 95 per cent of the cases of occlusive disease of the arteries are accounted for by these three diseases. In the remaining 5 per cent are included a small number of unusual forms of obliterative arteritis, types which at present are of greater pathologic than clinical interest: aneurysm with thrombosis, cervical rib with thrombosis of the peripheral artery and an irregular form, present in a small number of cases, which for lack of a better term has been designated simple thrombosis.[2] It was recognized that the last-mentioned group of diseases probably represented a clinical entity, but until a sufficient number of cases were observed, the pathologic picture was studied and the course of the disease was followed over a period of years it would be impossible to attempt to make an intelligent classification.

The following clinical description is fairly typical for this group of diseases: The patient who has sudden occlusion of one of the larger arteries of the extremities is usually an active adult. If thrombosis is massive and progressive, the usual signs of arterial insufficiency appear: ulcers or frank gangrene. In addition to the arterial lesions, the superficial or deep veins may be thrombosed. The process then may become stationary, with the development of an adequate collateral circulation, or it may become progressive, and the patient may lose an extremity. Other vessels may become thrombosed in addition to those in the limbs, namely, the cerebral, renal and coronary vessels. Phenomena of infarc-

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* Dr. Brown of the Division of Medicine, the Mayo Clinic, died on Nov. 28, 1935.

1. Buerger, Leo: The Circulatory Disturbances of the Extremities Including Gangrene, Vasomotor and Trophic Disorders, Philadelphia, W. B. Saunders Company, 1924.

2. Brown, G. E.; Allen, E. V., and Mahorner, H. R.: Thrombo-Angiitis Obliterans: Clinical, Physiologic and Pathologic Studies, Philadelphia, W. B. Saunders Company, 1928.

tion may occur in the kidneys, lungs and spleen. After a variable length of time and after complete subsidence of all symptoms a relapse may occur. No primary disease may be found to explain this thrombosing tendency. Neither polycythaemia vera nor any blood dyscrasia is found to be present. The pathologic changes in the vessels seem fairly characteristic and are of a bland, nonreactive form. There is usually only a slight reaction in the wall of the vessel or none. The pathologic picture does not in any respect resemble the usually recognizable type. There is no demonstrable disease in the tunics of the blood vessels, as thrombosis takes place in robust and active subjects, which rules out the slowing of the blood flow in the arteries as an etiologic factor. The major pathologic process seems to involve the stability of the suspension of the blood platelets rather than disease of the blood vessels.

The fairly characteristic clinical course in the five cases which form the basis of this report and the finding of certain variations in the coagulating properties of the plasma associated with these episodes of thrombosis led us to believe that we were dealing with an entity.

METHOD OF STUDYING THE COAGULABILITY OF THE BLOOD

The test for determining the coagulability of the blood is based on the ability of the oxalated plasma to clot on the addition of solution of calcium chloride. This is the original test of Howell, termed the prothrombin test. In two previous reports [3] a standardization of this test was reported on, and its interpretation and value were discussed. It was demonstrated that this test does not determine the prothrombin value but that it is a general test for the coagulability of the blood; consequently we have termed it a test for determining the coagulability of the plasma.

After venipuncture 4.5 cc. of blood is withdrawn in a cleaned and slightly oiled syringe and added to 0.5 cc. of a 1 per cent solution of potassium oxalate in a test tube. The test tube is allowed to stand for a couple of hours, in order to obtain a relatively clean plasma after sufficient sedimentation of the erythrocytes has taken place. With a capillary pipet 0.2 cc. is removed from this plasma layer to a Wassermann test tube, which is placed in a water bath at a constant temperature of 37.5 C. To this plasma is then added 0.2 cc. of a 0.5 per cent solution of calcium chloride. This addition will start the process of coagulation. The point at which the test tube can be turned upside down without the loss of any of its contents is considered the end-point. The time between the addition of the solution of calcium chloride and the end-point, which is measured with a stop-watch, is considered the coagulation time of the plasma. The average normal coagulation time is found to be two hundred seconds. In order to obtain comparative values, we have preferred to express the results of studies of coagulability in the form of an index, which is arrived at by dividing the average coagulation time of normal plasma by that of the patient's plasma. If the coagulation time of the patient's plasma is prolonged in relation to the normal, the index will be less than 1. This is a typical finding in cases of hemophilia, in thrombo-

3. Nygaard, K. K.: Coagulability of Blood Plasma, Proc. Staff Meet., Mayo Clin. **7**:544-548 (Sept. 21) 1932; Coagulability of Blood Plasma: Remarks on the Technic of Its Determination, ibid. **9**:151-156 (March 7) 1934.

cytopenic purpura and in jaundice in which there is a hemorrhagic tendency. The index will be higher than the average normal index of 1 when the coagulation time of the plasma is shortened in relation to the average normal time.

REPORT OF CASES

CASE 1.—A man aged 27 of Scandinavian descent was admitted to the clinic on Feb. 18, 1932. He had gonorrhea in 1923 but otherwise had been in good health until four days before his admission to the clinic. For many years he had been smoking one package of cigarets daily. There was no history of rheumatic fever or of symptoms of an early stage of heart disease.

On February 14, while walking down the street in the morning on his way to work, the patient was suddenly seized with extreme pain in both legs which caused him to fall to the ground. Dry heat was applied, and his legs, which looked white and were cold, were massaged for two hours. The left leg then regained its normal color, and he was able to move it normally. The lower portion of the right leg, however, remained blanched, and there were episodes of severe pain and impairment of the motor function.

At the time of the patient's admission to the hospital he weighed 155 pounds (70.4 Kg.). Ten months previously he had weighed 135 pounds (61.3 Kg.). The temperature in the morning ranged from 99 to 102.8 F., and the pulse rate ranged from 90 to 120 beats per minute. The blood pressure in millimeters of mercury was 118 systolic and 78 diastolic. The boundaries of the heart were found to be within normal limits. The cardiac rate was regular, and the tones were found by auscultation to be normal.

TABLE 1.—*Pulsations in Various Arteries in Case 1* *

Artery	Right	Left
Brachial	4	4
Radial	2 (?)	4
Ulnar	4	4
Femoral	0+	4
Popliteal	..	4
Dorsalis pedis	..	0
Posterior tibial	..	0

* In the following tables 0 denotes no pulsation, and 4 denotes normal pulsation.

On examination of the lower extremities the left leg appeared normal and did not change in color on elevation or dependency. There was a yellowish-appearing dry gangrene of the entire foot, and proximal to this was an area of gangrene of the first stage which reached up to the knee on the medial side, 2 or 3 inches (from 5 to 7.6 cm.) higher than on the lateral side. The pulsations in the various arteries are tabulated in table 1.

The patient looked sick and toxic. At operation, which was not performed until seven days after the patient's admission to the hospital and eleven days after the acute arterial occlusion, amputation was carried out at the junction of the middle and the lower third of the right leg. The femoral artery was found to be filled with a soft clot, which dropped out easily.

Prior to operation the patient had a moderate degree of tachycardia while in the hospital. After operation the temperature continued to vary between 99 and 101 F. for one week, rising on one occasion to 102.8 F. in the evening of the fourth postoperative day. After the first week the temperature subsided

somewhat and remained lower for two or two and a half weeks. The tachycardia, however, continued after operation, the pulse rate varying between 120 and 130 beats per minute. At the end of the third week the pulse rate gradually fell to between 80 and 100 beats per minute. An electrocardiogram taken the day before operation was essentially negative. This preoperative tachycardia was explained on the basis of toxemia due to the gangrenous leg. On the fourth day after operation pain developed, and a friction rub was heard over the entire precordial region. An electrocardiogram taken the following day indicated complete bundle branch block on the left. In two days the precordial pain disappeared, while the friction rub at the base still persisted for another day or two.

The patient felt fairly well after the operation until the seventh postoperative day, when he suffered an attack of pain in the left groin. A diagnosis of thrombosis of the left femoral vein was made.

On the twenty-eighth day after operation the patient complained of sudden pain in the small of the back and in the region of the left kidney. The first specimen of urine examined contained a large number of erythrocytes and a large amount of albumin. The value for urea was 42 mg. Hematuria lasted all the time the patient stayed in the hospital, ninety-nine days after operation. For a few days following the onset of the pain in the renal region the specimens of urine contained a few granular and hyaline casts, which, however, later disappeared almost entirely. The blood urea values did not at any time show marked changes. On the forty-fourth postoperative day the phenolsulfonphthalein test indicated an excretion of only 35 per cent in two hours. The value for serum sulfates varied between 6.6 and 7.6 mg. per hundred cubic centimeters. It was evident that the patient was suffering from renal insufficiency, and appropriate treatment was given. At no time did the observation of variations in the blood pressure indicate the presence of any hypertension. Examinations of the ocular fundi revealed no abnormality.

On the thirty-seventh day after operation the patient complained of pain in the calf of the left leg. A diagnosis of thrombosis of the short saphenous vein was made. On the forty-ninth day pain developed in the region of the left elbow, with all the evidence of thrombosis of the left basilic vein. On the fifty-first postoperative day a diagnosis was made of thrombosis of the right basilic vein and thrombosis of the superficial vein of the inner portion of the left thigh. The following day pain developed in the left popliteal region, with induration and tenderness of the popliteal vein.

Three days later, on the fifty-fifth postoperative day, there was thrombosis of a superficial vein in the abdominal wall in the right lower quadrant. After the sixty-first day there was extension of the thrombotic process in the basilic veins on both sides, both in a proximal and in a distal direction. During these episodes of thrombosis there had been practically no rise in the body temperature and little if any local inflammatory reaction.

During the following two or three weeks there still were signs of small recurrent migrating regions of thrombosis in the superficial veins, especially of the arms. At this time there was a marked improvement in the patient's general condition. An investigation of the urinary tract was undertaken in order to determine the source of the hematuria. A pyelogram revealed that the right and left calices, pelves and ureters were normal. The source of the microscopic hematuria could not be ascertained. The patient left the hospital on June 1, ninety-nine days after amputation of the right leg.

The patient returned for another examination on September 1 of the same year. Although he had not been doing any work, he had been feeling well since his dismissal from the hospital. There had been no recurrence of thrombosis. The results of examination of the arteries at this time are given in table 2.

TABLE 2.—*Pulsations in Various Arteries in Case 1 at the Second Examination*

Artery	Right	Left
Brachial	4	4
Ulnar	4	4
Radial	2	4
Femoral	0	4
Popliteal	..	4
Dorsalis pedis	..	2
Posterior tibial	..	0

TABLE 3.—*Pulsations in Various Arteries in Case 1 at the Third Examination*

Artery	Right	Left
Brachial	4	4
Ulnar	4	4
Radial	2	4
Femoral	0	4
Popliteal	..	4
Dorsalis pedis	..	2
Posterior tibial	..	3

TABLE 4.—*Coagulability of the Plasma and the Platelet Counts in Case 1*

Date	Index of Coagulability*	Platelets per Cu. Mm. of Blood	Comment
12/13/32	...	.....	Acute occlusion of second, third and fourth fingers of left hand; thrombosis of right basilic vein
12/27/32	...	.....	Admitted to clinic
12/28/32	1.4	875,000	
1/ 4/33	0.9	357,000	
1/ 9/33	0.8	352,000	
8/23/33	...	.....	Second admission; large ulcer due to stasis
8/28/33	0.6	280,000	
2/ 1/34	...	.....	Recurrent occlusion of first toe on left foot
3/ 5/34	1.2	475,000	
9/28/34	...	.....	Occlusion of fourth finger of left hand
10/ 3/34	...	.....	Occlusion of first toe of each foot
10/ 4/34	1.4	325,000	
10/ 9/34	1.1	419,000	
10/19/34	0.9	355,000	
10/26/34	0.9	350,000	
10/30/34	...	.....	Fourth finger of left hand and first toe of each foot amputated
11/16/34	1.2	312,500	
11/10/34	0.8	365,000	

* The average index value for normal subjects is 1.

On April 28, 1933, the patient returned for a third examination. There were no complaints. There had been no recurrence of thrombosis. Results of the examination of the pulsation of the arteries at this time are given in table 3. This examination indicated definite improvement in the circulation of the left leg.

At this time there was persistent hematuria. A combined intravenous phenolsulfonphthalein test revealed a return in two hours of 65 per cent. The general examination otherwise did not reveal anything of significance.

A letter was received from the patient's sister stating that he had died on March 1, 1934, at a hospital in the South, where he had gone to spend the winter. It was later found that he died of pulmonary embolism.

Comment.—One thing is obvious in this case—the condition is to be classified as belonging to the group of organic obliterative diseases of the arteries. Arteriosclerosis is ruled out because of the age of the patient, the clinical examination and the microscopic examination of the arteries from the amputated leg (fig. 1), which did not reveal degenerative changes in the arterial wall. The patient belonged to the age group characteristic of thrombo-angiitis obliterans. Against a diagnosis of thrombo-angiitis obliterans, however, was the patient's

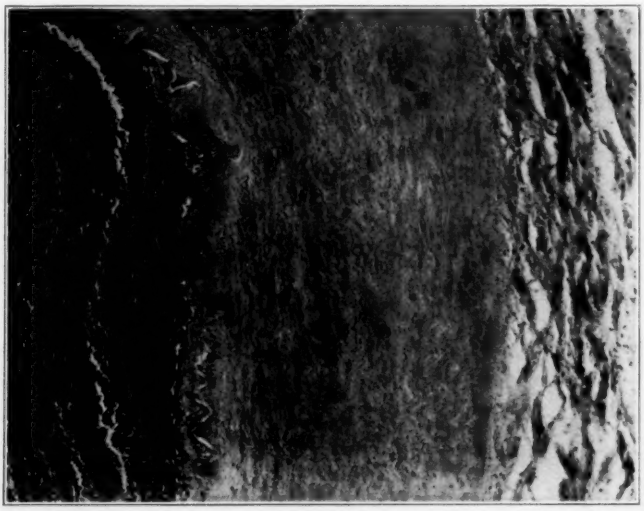

Fig. 1 (case 1).—Part of the right femoral artery, showing little cellular reaction in the media and adventitia. The thrombus occluding the vessel is of the bland, nonorganized type.

history before the onset of the disease. There was nothing in this history to indicate that he had ever had any subjective or objective symptoms of arterial insufficiency before the acute onset of the disease. There had been no signs of superficial phlebitis. Microscopic examination of the resected vein (fig. 2) did not show the inflammatory changes characteristic of lesions of the veins in thrombo-angiitis obliterans. The most difficult problem in this case was the question of the nature of the acute occlusion of the femoral artery. One could assume that an embolus or thrombus in the bifurcation of the iliac arteries struck without warning at the time of the acute onset, and it is possible also that

the temporary absence of pulsation in the arteries of the left leg was due to spasm. At the time of the patient's admission to the hospital it was difficult to see how the heart could have been the source of the embolus; so far as could be made out at that time no demonstrable pathologic change was present in the heart, and the previous history did not indicate any trace of the presence of a cardiac lesion. The onset of acute pericarditis four days after amputation, with persistent tachycardia before as well as three weeks after amputation, suggested the presence of some obscure cardiac lesion. One suggestion was localized myocardial infarction, with mural thrombosis and subsequent pericarditis over

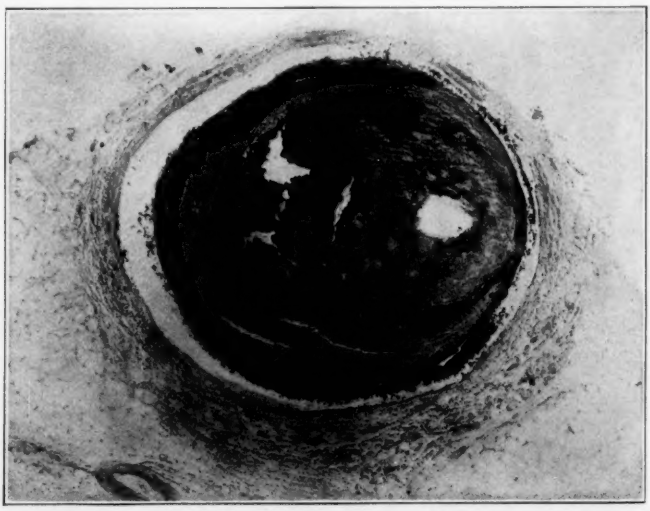

Fig. 2 (case 1).—A thrombosed superficial vein from the abdominal wall.

this lesion. This, however, is purely a conjecture and a dubious one, because of the absence of any subjective cardiac symptoms before the acute arterial occlusion of the leg.

At the time of the patient's admission to the hospital the embolic nature of the occlusion was questioned, for the reason that the pain which he suffered did not seem to be of the extremely severe nature seen in typical cases of acute embolic arterial occlusion. Therefore the possibility was discussed that the patient might have had a thrombus form in situ, which had led to acute arterial occlusion. It is difficult to believe that in a large artery, with no injury to the wall of the vessel and a rapid flow of blood, there is much chance for a thrombus to form, and we readily admit that such a hypothesis in this case must be advanced with reservations. Irrespective of the stand one takes as to

the cause of the original occlusion, one is impressed with the fact that there was a marked tendency toward thrombosis of the veins in this case, which was evidenced by the development of seven active stages of thrombosis in addition to several small migrating regions of thrombosis in the veins. This patient, therefore, appeared to have had a tendency toward thrombosis, and microscopic study of a specimen removed from the thrombosed vein for biopsy did not disclose an inflammatory condition that could be thought to be responsible for such a tendency.

These clinical and pathologic investigations were supplemented by studies of the protein content of the serum and of the coagulability of the blood plasma (fig. 3). The figure indicates that while the patient

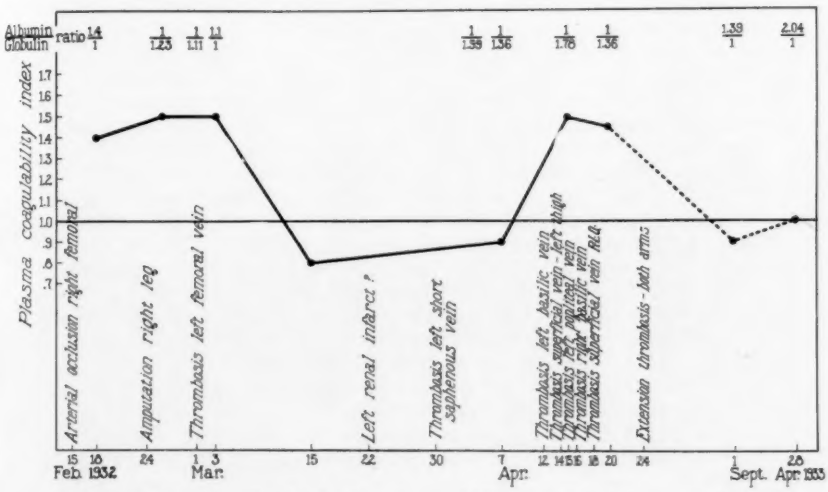

Fig. 3 (case 1).—Graph showing the variability of the plasma coagulability during thrombosing episodes.

remained in the hospital there were two periods during which there was demonstrated a high degree of coagulability of the blood plasma and that the active phases of the formation of thrombi fairly accurately coincided with these two periods of a high degree of coagulability. Searching for a more definite quantitative change in the blood, it was found, as is indicated by the figure, that after the first day in the hospital the patient had an almost constant inverse albumin-globulin ratio. The distribution of the serum proteins was in favor of the less stable proteins, mainly the globulin-fibrinogen fraction. It is too early to debate the etiology and the consequences of these quantitative and qualitative changes in the blood. The impression, however, remains that

this was a case in which the most outstanding clinical picture was one of vascular thrombosis in microscopically normal vessels and, further, that this was a case in which changes in the coagulability of the blood plasma and in the distribution of the serum proteins seemed to coincide with periods of active thrombus formation.

CASE 2.—A hardware merchant aged 49, of English and Scotch descent, was first admitted to the clinic in February 1925. He had been in the habit of smoking three or four cigars a day. At the age of 21 he contracted gonorrhea, which was complicated by swelling, pain and stiffness of both knees and ankles of seven weeks' duration. Four years later he had recurrence of the pain, redness and swelling of both knees and of the joints of both feet. After that he had repeated attacks of arthritis. The diagnosis at this time was chronic infectious arthritis of both knees, both ankles and the metatarsophalangeal joints.

The patient returned to the clinic in December 1932. In September of that year he had slight pain in the calf of the left leg for a few days. In the latter part of October he was seized with severe pain in the left flank, followed after a short while by frequent and urgent urination, with passage of bloody urine, and by frequent stools. Gross hematuria lasted for three days and then cleared up gradually and never returned. On November 8 the patient noted pain and swelling of the third finger of the right hand, associated with swelling of the back of the hand. The finger was cold. This condition lasted for about a week.

On December 13 the patient noticed that the index and second and third fingers of the left had were bluish; they later turned white, and a high swelling developed on the dorsum of the left hand. This swelling gradually disappeared, and the fingers regained their normal color in the course of a week. The skin, however, turned black over an area the size of a half-dollar, situated on the dorsum of the second metacarpophalangeal joint. This incident was accompanied with severe chilling sensations on the first day, but fever was not present. At the same time the patient noted the onset of tenderness along the right basilic vein, which extended up to the right shoulder, with some redness along the vein.

On admission to the hospital in December 1932 the patient weighed 160 pounds (72.6 Kg.), as compared with his normal weight, 173 pounds (78.5 Kg.). He felt fairly well. The blood pressure in millimeters of mercury was 130 systolic and 70 diastolic; the pulse rate was 80 beats per minute, and the temperature was 98 F.

On physical examination there was no detectable pathologic change in the lungs or heart. The extremities gave evidence of the same arthritic changes as on the first examination in 1925. In addition, there was a necrotic area of skin over the base of the left index finger. There was also subsiding thrombosis of the right basilic vein. All the palpable vessels were found to be open. Examination of the eyes showed normal fields, with the media clear. The fundus of the right eye was normal; in the left eye there was resolving thrombosis of the central veins and artery, especially the temporal branches.

The blood was normal. Cultures did not yield any bacterial growth after forty-eight hours. Flocculation tests gave negative results. Roentgenograms of the left forearm and hand were negative. A simple roentgenogram of the kidneys, ureters and bladder did not reveal any shadows indicative of stone in the urinary tract. After a few days in the hospital, with local treatment of the necrotic area of the skin of the left hand, the patient went home.

The patient returned on Aug. 23, 1933. The condition of his hands had gradually improved. One morning in February he noticed pain in the left calf. The next day some brownish black blisters appeared over the anterior medial surface of the left leg above the ankle and resulted in the formation of an ulcer, which persisted up to the time of his third admission to the clinic. During each day swelling developed around the left ankle, extending up to the knee, but he continued his work and was on his feet every day. No definite varicosities of the veins could be seen, except one small one above the left knee. A diagnosis was made of ulcer due to stasis secondary to thrombophlebitis. The patient was put to bed, and the edematous fluid was drained off by elevation of the limb. A skin graft was performed on September 11. After this the wound healed nicely, and the patient was dismissed on October 2.

In December 1933 the patient suddenly noted severe pain and cyanosis in the first toe of the left foot. The pain lasted for four or five hours, and then the condition cleared up completely. On Feb. 1, 1934, a sudden pain was noted in the same toe, but it cleared up in two days.

The patient returned to the clinic on March 5. All the arteries of the extremities pulsated normally. The fundus of the right eye appeared normal; in the left eye it was evident that collateral circulation had been established following thrombosis of the central retinal vein. The inferior temporal vein had remained occluded, together with the accompanying artery. There was some scarring along the superior temporal vein and artery, and a small residual hemorrhage was seen posteriorly, in the macular region.

Aside from these findings, physical examination at this time did not reveal anything different from what had been found at the previous examinations. The coagulability of the plasma and the number of platelets indicated conditions within normal limits. After a short period of hospitalization the patient was dismissed with a sponge compression over the ulcerated area and a heavy rubber bandage.

His general condition after leaving the clinic apparently was satisfactory until September 1934, when there was sudden and rather severe pain and coldness in the fourth finger of the left hand, followed by a bluish discoloration that gradually involved the whole finger and nail. Marked swelling of the entire hand also occurred. On November 3 the nail on the fourth finger came off; there was a gradual development of gangrene, and blebs formed on the finger, with sloughing of the skin, leaving a denuded finger. A few days after this episode of acute occlusion in the hand the patient's feet felt cold, and he felt a hot burning pain in both large toes. These toes were completely blue and somewhat swollen. The patient reentered the clinic a few hours later. He had had at different times during the previous nine months three or four similar episodes, without any resultant ulceration.

On examination at this time the patient was found to be afebrile, a condition in which he remained throughout his stay in the hospital. The blood pressure was normal. Physical examination showed that the heart was normal. The entire fourth finger of the left hand was in a stage of dry gangrene (fig. 4*A*). Large bluish blisters covered most of each big toe (fig. 4*B*), which appeared to be in a stage of gangrene. The feet felt very warm to the touch, whereas the toes felt only moderately warm. All the palpable arteries in the feet and hands were open.

The leukocytes numbered 5,300 per cubic millimeter of blood. The differential count was normal. The total serum protein content was 4.71 Gm. per hundred cubic centimeters, the albumin fraction 1.8 Gm., giving an albumin-globulin

ratio of 1:1.6. Flocculation tests were negative. The first specimen of urine revealed a few erythrocytes and pus cells (grade 3). The hematuria remained unchanged during the patient's stay in the hospital. Studies of the plasma on his first day in the hospital showed a platelet count of 325,000 per cubic millimeter, with an index of coagulability of 1.3.

The general condition of the patient was good. There was no systemic reaction or toxemia, and there was almost complete absence of pain. On October 26 amputation of both big toes and the fourth finger of the left hand was performed under local anesthesia.

Comment.—The patient had had chronic infectious arthritis, which was completely inactive, leaving residual impairment of the joints. With this exception he was in excellent health. The question arises whether this arthritis could stand in any causal relationship to the recurrent episodes of thrombosis. The evidence is against this, however, first, because disease of the blood vessels is not observed in the course of

Fig. 4 (case 2).—*A* shows the left hand and *B*, the feet at the time of the patient's admission to the clinic.

arthritis, and, second, because too long an interval elapsed between the active period of arthritis and the onset of the thrombosing disease. The absence of clinical evidence of arteriosclerosis, supported by the fact that degenerative changes were not observed in the involved vessels, excluded arteriosclerosis as the etiologic factor in this case.

In about 5 per cent of cases of thrombo-angiitis obliterans occlusion of the digital arteries is observed, with normal pulsation of the arteries of the wrist and foot. Against the diagnosis of thrombo-angiitis obliterans in this case, therefore, was the widespread nature of the thromboses, the process including the retinal arteries and veins, and the nonreactive nature of the phlebitis and the arteritis, as observed clinically. The microscopic picture of the vascular lesions of the digital arteries and veins did not resemble in any respect the inflammatory changes seen in cases of thrombo-angiitis obliterans.

The nondemonstration of any source of an embolus, the long period of observation and the identical situation of thrombi in the consecutive episodes of occlusion do not favor the diagnosis of a condition of embolic origin. The pertinent facts in this case were episodes of arterial and venous thrombosis involving the left short saphenous vein, the arteries of the fingers and toes, the right basilic vein and the central retinal artery and vein and possibly renal infarction also. The impression is strong that this process was on the basis of a recurring thrombosis not attributable to disease of the blood vessels.

As will be seen in table 4, studies of the coagulability of the plasma and the platelets gave evidence of a moderately increased coagulability on two occasions, namely, fifteen days after the episode of arterial occlusion and thrombosis of the vein in December 1932 and on the day after occlusion of the arteries of both great toes (Oct. 3, 1934). Only during the first episode was a high platelet count encountered. In table 4 is given also the date of the episodes of thrombosis. These studies reveal some correlation between the episodes of thrombosis and the changes in the coagulating properties of the plasma. There was a cyclic behavior in the coagulability of the plasma, periods of rapid coagulation being followed by a return to normal or to subnormal levels.

Case 3.—A barber, an American Jew aged 47, was admitted to the clinic on Aug. 29, 1932. For several years he had been a heavy smoker (from twenty to forty-five cigarets a day). Until 1928 he had enjoyed excellent health; from that time, however, his feet and legs had begun to tire easily when he walked around in the barber shop. At no time, however, had he suffered pain or claudication, and he had not had superficial phlebitis. This tiredness of his legs and feet had progressed slowly. In 1930 his toes had become red and had burned and pained, usually at night. These sensations had been partially relieved by immersion of the feet in cold water. Relief had not been obtained on elevation of the feet. Various kinds of weather had not affected these sensations.

In November 1931 the patient accidentally injured the small toe of the left foot, sustaining an abrasion, which had not healed. His local physician diagnosed the condition as thrombo-angiitis obliterans. After five injections of typhoid vaccine the ulcer on the toe healed. On April 23 the patient was suddenly taken ill with severe abdominal cramps associated with fever, nausea and vomiting. This condition lasted for eight hours, whereupon the patient was taken to a local hospital, where an exploratory operation was performed. He was then informed that he had acute pancreatitis and that the capsule of the pancreas had been split. The postoperative course was uneventful, and the patient was dismissed in good condition. His feet, however, continued to bother him. About Aug. 1, 1932, a small blister developed on the small toe of the right foot, followed by a nonhealing superficial ulcer. A dependent position of the foot had given the most relief.

When the patient was admitted to the clinic his temperature was 98.8 F., and he remained afebrile during his stay in the hospital. The pulse rate and the blood pressure were normal. The fourth toe of the left foot was in a pregangrenous stage, and there was also a superficial pregangrenous area at the

base of the small toe of the right foot. There was mild rubor of the toes on dependency and mild blanching on elevation. There were no clinical signs of arteriosclerosis. All the palpable arteries were pulsating. Examination of the eyes and fundi revealed an essentially normal condition. Neurologic examination gave essentially negative results.

The most significant finding in this case, besides the condition of the toes, was a sharp increase in the platelet count and in the volume and coagulability of the plasma. The hemoglobin content of the blood was 15.2 Gm. per hundred cubic centimeters, the erythrocytes numbered 4,520,000 and the leukocytes 17,800 per cubic millimeter. The reticulocytes amounted to 1 per cent; the differential count was essentially normal, and examination of blood smears revealed leukocytes that had undergone moderate toxic changes. The platelet count was 2,480,000 per cubic millimeter on Aug. 31, 1932, and at the same time the platelet volume was 2.21 per cent, as compared to a normal value of approximately 0.4 per cent, according to the Van Allen method. This determination was repeated the next day for purposes of establishing a control, an average of two observations showing a platelet count of 2,450,000. Urinalysis revealed no abnormality. The index of coagulability of the plasma was 1.5.

Amputation of the fourth toe of the left foot was advised, but the patient refused operation. After a few days of medical treatment he was dismissed and advised to continue treatment at home. We were in communication with his local physician for two years, and the last we heard was that the patient was doing well and was working every day.

Comment.—The original diagnosis in this case was thrombo-angiitis obliterans. There were normal pulsations in the usually palpable arteries. The marked thrombocytosis and disturbance in coagulability, however, necessitated further consideration, as these changes have never been observed in a large series of cases of thrombo-angiitis obliterans and arteriosclerosis obliterans. The clinical symptoms and signs in this case, when viewed critically, were not entirely characteristic of those of thrombo-angiitis obliterans. The prethrombotic symptom of fatigue of the feet when standing was not that of claudication, nor was the burning distress of the feet, with an increase in the local temperature, a symptom of thrombo-angiitis obliterans.

There were several episodes of thrombosis of the digital arteries of the feet during a period of nine months. There was no evidence of phlebitis, and the major arteries did not become occluded within two years. The provisional diagnosis of thrombo-angiitis obliterans of an irregular type therefore was made. Embolism could be ruled out on the basis of the findings and subsequent course. As the platelet count was enormously high and there was an increase in the coagulability of the blood plasma, however, considering that there are similar clinical and hematologic findings in other irregular types of arterial occlusive disease, it seems warranted to include this case in the group of cases of thrombosing disease, in spite of the fact that it was not possible to study the involved arteries microscopically.

It is unfortunate that we have not had an opportunity to examine this patient again and have not been able to obtain information concerning the present condition of his blood. Such an examination would show whether the thrombocytosis found at the time of his visit to the clinic in 1932 was still persisting. There is the possibility that this patient had that rare form of leukemia called thrombocythemia, in which only the thrombocytopoietic apparatus undergoes proliferative changes, leading to an enormous outpouring of thrombocytes. If this was the case, the arterial disease should be considered as secondary to the disease of the blood. Without wishing to stress this part of the discussion, however, it seems reasonable to consider the problem from a different angle. In April 1932 the patient had an attack of severe abdominal pain, for which an emergency operation was undertaken the same day. The surgical diagnosis was that of acute pancreatitis. In August of the same year, when he was examined at the clinic, the thrombocyte count was so high as to lead one to believe that splenectomy had been performed, an assumption which, of course, was not in accord with the facts. The question then remained whether the patient did not suffer from "functional splenectomy." In other words, had thrombosis of the splenic artery or vein taken place at the time of the onset of the acute abdominal disease, and if so had this thrombosis extended also into the arteries of part of the pancreas, thereby cutting off part of its blood supply and consequently resulting in acute pancreatitis?

These of course are only conjectures which will remain unanswered. In a consideration of the whole clinical picture of this disease, however, such possibilities are of more than pure academic interest. They open up the way for the assumption that in this case the acute pancreatitis and the pregangrenous condition of the toes may be regarded as of the same pathogenesis as the arterial occlusion. The pancreatitis and condition of the toes will consequently have to be considered as two clinically different, but pathogenically identical, pictures of the same disease.

CASE 4.—A rural mail carrier aged 53, a gentile, was in good health until February 1932, when while trying to close a garage door he felt sudden numbness and severe pain in his left hand. This hand turned white and felt paralyzed. In the course of two weeks the color of the hand returned to normal.

In January 1933, while the patient was walking, the left foot suddenly became weak and cold, with severe pain and numbness. After approximately twenty-four hours the foot regained its normal appearance. For about six months, however, there was persistent though moderate pain in the left big toe, especially on walking. On April 15, while resting, the patient suddenly became extremely dizzy and immediately afterward vomited. With assistance he was able to walk to his bed, where he stayed for eight weeks. Any attempt at sitting up in the first six weeks was followed by dizziness and by a tendency to fall to one side. After the acute attack he had diplopia and dimness of vision and for some time had difficulty in swallowing. He was not able to sneeze or cough. These con-

ditions, however, gradually cleared up. For one month after the onset he was insensitive to heat and cold over the right side of the body and over the left side of the face. After eight weeks in bed he got up and gradually recovered.

In the latter part of June 1933, three weeks before his admission to the clinic, the patient was walking a few steps when his right foot suddenly became numb and turned white and cold. Gangrene of the right foot developed. At no time was there intermittent claudication, superficial phlebitis or ulcer formation in the extremities.

On admission to the clinic on July 20, 1933, the patient was found to be in good general condition; he had no fever, and his blood pressure was normal. He remained afebrile the three days he stayed in the hospital before an operation was performed. The left eye was held slightly closed, although there appeared to be no actual ptosis. The pupils were equal and reacted to light and in accommodation. There was a marked hoarseness owing to fixation of the left vocal cord. There was dry gangrene of the entire right foot. The left foot showed a moderate degree of pallor on elevation and a slight degree of rubor on dependency. A

TABLE 5.—*Pulsations in Arteries in Case 4*

Artery	Right	Left
Brachial	4	0
Radial	4	0
Ulnar	4	0
Femoral	4	4
Popliteal	0	4
Posterior tibial	0	0
Dorsalis pedis	0	0

TABLE 6.—*Coagulability of the Blood in Case 4*

Date	Index of Coagulability	Platelets, per Cu. Mm.	Platelet Volume, Cc. per 100 Cc. of Blood
7/21/33	1.7	380,000	0.43
7/26/33	1.7	337,500	0.40
8/ 7/33	1.4	415,000	0.45

similar postural change in color was found to be present in the left hand, indicating an insufficiency in the arterial blood supply, the extension of which was easily determined by examining pulsations of the palpable arteries (table 5).

The routine laboratory examinations did not reveal anything of essential importance. The total serum protein content was 6.1 Gm. per hundred cubic centimeters, with an albumin-globulin ratio of 1.44:1. The index of coagulability of the plasma on the day of the patient's admission to the clinic was found to be 1.7, as compared with the average normal index of 1, indicating a marked increase in the coagulability of the blood. The platelet count was normal (380,000 per cubic millimeter), with a platelet volume within the normal range (0.43 cc. per hundred cubic centimeters of blood). A study of the coagulability of the blood during the patient's stay in the hospital is given in table 6. An electrocardiographic tracing indicated a normal condition of the conductive system of the heart.

After the patient had been in the hospital for three days, amputation of the extremity through the lower part of the right femur was performed. The postoperative course was uneventful, and the patient was dismissed on the

fifteenth day after amputation. Letters from his local physician indicate that he is doing satisfactorily. There has been no further episode of arterial occlusion.

Microscopic examination of the occluded artery removed at the time of operation revealed some interesting features, as may be seen in figure 5 *A* and *B*. The absence of degenerative processes in this artery argues against a diagnosis of arterial occlusion as the basis of a local process of arteriosclerosis. This artery was occluded by a nonorganized thrombus, and the arterial wall showed no inflammatory reaction. There was no periarterial inflammation. We must conclude from the microscopic observation that this process was different from thrombo-angiitis obliterans or from arteriosclerosis.

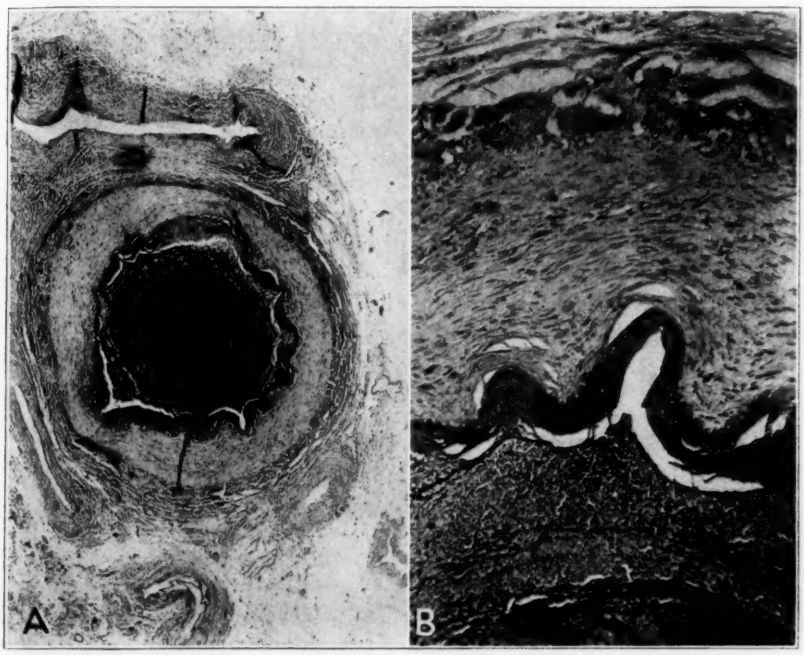

Fig. 5 (case 4).—The main artery from the amputated right leg. The vessel is completely occluded by a cellular nonorganized clot. There is no cellular reaction in the vessel, except for slight infiltration of the adventitia. *A*, × 15; *B*, × 65.

Comment.—There can be but little doubt as to the diagnosis in this case. Within eighteen months the patient had four acute arterial occlusions, the first one involving the arteries of the left hand, the second involving the arteries of the left foot, a third involving an artery of the central nervous system (left inferior cerebellar artery?) and a fourth involving the arteries of the right foot, which led to gangrene necessitating amputation.

As to the clinical diagnosis in this case, again the condition is one of the irregular forms of obliterative disease of the arteries. The patient belonged to the "early arteriosclerotic" age group. Clinical examination, however, did not reveal any signs of general distribution of arteriosclerosis. Microscopic study of the involved artery did not reveal any arteriosclerotic disease. It seems justifiable, therefore, to consider the arterial occlusive disease in this case as not being on the basis of arteriosclerosis; nor does it come under the head of thrombo-angiitis obliterans, for several reasons. Superficial phlebitis had never occurred, and there was no history of subjective symptoms of insufficiency of the arterial blood supply, such as intermittent claudication, changes in color or ulceration, before the episodes of arterial occlusion. Acute thrombo-angiitis obliterans may show a similar course, but in this case no other arteries were found to be involved save the ones acutely occluded. In addition, involvement of an artery of the central nervous system, such as occurred in this case, argues against a diagnosis of thrombo-angiitis obliterans. The strongest argument against such a diagnosis, however, is afforded by the microscopic picture of the involved artery, which is definitely not that of thrombo-angiitis obliterans.

The sudden character of the occlusion would be more likely to signify embolism. The source of a possible embolus, however, could not be traced. The patient had never had any subjective symptoms of insufficiency or other cardiac symptoms, and an objective examination did not reveal any symptoms which indicated the presence of a cardiac lesion. An electrocardiogram excluded abnormalities in the conductive system.

In this case we are again left with the impression that we are dealing with a condition of an irregular type, irregular in the respect that it does not fit into any of the groups of arterial occlusion which by clinical and pathologic experience we have learned to distinguish. By this process of elimination, therefore, and strongly supported by the positive findings of a marked increase in the coagulability of the blood, we were led to the conclusion that this may be considered among the cases of thrombosing disease.

CASE 5.—A 40 year old woman of English descent was admitted to the clinic on Sept. 30, 1924. She had enjoyed good health up until the time of her marriage at the age of 21. She had two living children and had had three pairs of twins, all of whom had been stillborn after from five to eight months of intra-uterine life. After the patient's last infant was born, seven years prior to her admission to the clinic, she had thrombosis of the left femoral vein. Four years later she suddenly felt dizzy and had to be helped to a chair. From there she fell to the floor in a state of semiconsciousness. For several days there were similar attacks. She noticed that her left arm and leg were paralyzed. She was brought home and put to bed, where she stayed for two weeks. After this time she began to sit up but was unable to walk around. During the year preceding her admission to the clinic she was able to walk with crutches. Since the onset of

hemiplegia there had been little improvement. In February 1924, seven months before her admission to the clinic, the patient awakened one night with severe pain in the right shoulder, elbow and hand. The whole arm prickled, as if it were asleep, and for several hours appeared white. A week before her admission to the clinic she had a similar attack. The right hand was white for four hours, and there was severe pain in the whole arm, associated with numbness; this had persisted more or less ever since.

The main reason the patient was referred to the clinic was that the local physician suspected she had a tumor of the brain. Two weeks before her admission to the clinic she awakened from a sound sleep at 2 a. m. with a severe pain in the top of the head. For a week this headache kept her awake day and night, and she finally had to be given morphine.

On admission to the clinic the patient was afebrile. The action of the heart was rhythmic, and the rate was 88 beats per minute. The right pupil was a little larger than the left, which was slightly irregular. The reflexes were normal. The right fundus was not seen because of a capsular remnant of an apparently traumatic cataract of childhood. In the left eye the disk and macula appeared normal. The vessels appeared essentially normal. The heart, lungs and abdominal organs appeared normal in all respects on physical examination. Neurologic examination revealed the classic symptoms of left hemiplegia.

The right arm and hand appeared colder than the left. A blood pressure reading for the left arm indicated a systolic pressure of 118 and a diastolic pressure of 70, whereas no reading was obtained for the right arm. The brachial, ulnar and radial arteries of the right arm were not palpable. The arteries of the lower extremities were pulsating normally, and there were no signs of arteriosclerosis of the vessels. The mobility of the right arm was normal.

Flocculation tests were negative, as were also examinations of the spinal fluid. The value for hemoglobin was 9.2 Gm. per hundred cubic centimeters, and the erythrocytes numbered 3,640,000 and the leukocytes 11,700 per cubic millimeter of blood.

The severe headache and the objective and subjective symptoms in the right arm were not clearly understood. Further developments, however, cleared up the diagnostic difficulties. The patient had been in the hospital for six days when she had severe pain in the entire right arm. The hand turned white, with streaks of cyanosis. The finger-nails were blue. The lower half of the right forearm and the hand felt cold, whereas the rest of the arm felt warm. Examination of the capillaries of the nail folds the next morning revealed almost complete stasis in all the loops. It was apparent that the main artery to the right arm had become occluded high up in the arm. There was rapidly developing gangrene of this extremity.

The patient's general condition was poor and the prognosis grave. After considerable deliberation, amputation in the mid-upper portion of the arm was decided on; this was done with the area under local anesthesia seven days after the onset of acute occlusion. The patient died seventeen days after admission to the hospital and twelve days after the onset of acute arterial occlusion.

Postmortem examination revealed the following data: The heart weighed 337 Gm. The cardiac muscle was reddish brown and of firm consistency. No valvular vegetation or mural thrombi were present. The lower lobe of the right lung was congested; otherwise there was no demonstrable lesion in this lung. There was considerable congestion in the lower lobe of the left lung; in this portion, extending from the surface about 2 cm. into the lung, was an area 4 cm. in diameter which was firm and dark reddish blue. There was also a small

scar on the pleural surface, which on section revealed an old infarction 4 by 3 cm. in diameter. The pulmonary arteries were open and contained no thrombi. The pulmonary veins, however were occluded by thrombi. Examination of the right subclavian artery revealed an organized thrombus, which began at the opening of the subclavian artery into the aorta and extended throughout the vessel as far as it can be followed and also up into the right carotid artery. The thrombus was red and contracted and almost filled the lumen of the vessel. It was adherent throughout. The left femoral veins revealed an ancient thrombotic process. The postmortem observations were otherwise essentially negative.

Comment.—This patient at the time of her admission to the clinic presented a puzzling picture. Further clinical developments and the postmortem examination cleared up some of these difficulties. Even then, however, some questions remained unanswered. One thing was obvious; during the last seven years of her life, whenever she was sick, the patient had some associated lesion of the blood vessels. There was a clearcut history of puerperal thrombosis of the femoral vein; again, four years afterward, left hemiplegia developed, without obvious explanation. Three years after this the patient suffered repeated attacks of arterial occlusion. These events suggested the manifestations of a primary clinical entity. The patient's sister was said to have died of apoplexy while young. The patient had had repeated stillbirths. There was nothing, however, in the clinical and laboratory examinations which could give the faintest support for the suspicion that she had a syphilitic infection. She was comparatively young, the blood pressure was normal and there was no clinical or pathologic evidence of renal disease or arteriosclerosis. Her sex, the absence of superficial phlebitis and of a history of intermittent claudication, the cerebral involvement and finally the presence of normally pulsating arteries, except the arteries acutely involved, together with the noninflammatory character of the pathologic lesion (fig. 6 *A* and *B*), all argued against a diagnosis of thromboangiitis obliterans. The unusual forms of arteritis were ruled out by the pathologic appearance of the vessels.

Are the acute vascular episodes to be explained on the basis of the embolism? An embolus in an artery in the internal capsule is a reasonable assumption. Embolism would mean the formation of a thrombus somewhere in the arteries of the general circulation, in the left portion of the heart or in the pulmonary veins. Clinical examination, however, showed that the patient's heart was normal, and postmortem examination did not indicate the presence of any pathologic process which logically could have led secondarily to mural thrombosis. Still the hemiplegia may have been caused by an embolus of unknown origin, or it may have been due to thrombosis in situ in the internal capsule. The same two possibilities are met in regard to the episodes of acute occlusion of the arteries of the right arm. It is logical to assume that the last two episodes were the result of a process superimposed on the one

which caused the first symptoms of occlusion in February 1924. This final occlusion came on without previous symptoms and with the suddenness of embolism. If there was embolism and not thrombosis, it is doubtful that the heart gave rise to the embolus, for the reasons just mentioned. At the time of postmortem examination thrombosis was found to have taken place in the pulmonary veins, and this may easily have given rise to an embolus which partly blocked the subclavian and carotid arteries, with subsequent complete blockage of the circulation to the distal part of the right arm.

Fig. 6 (case 5).—An occluded artery from the right arm, showing a slight cellular reaction in the media and adventitia. The occluding thrombus is non-organized. *A*, × 50; *B*, × 185.

At necropsy no accurate microscopic studies were made of the pulmonary veins. We are therefore at a loss in tracing the character of the thrombus and its possible age as well as possible lesions of the vessel wall. We admit freely that this constitutes the weak point in the presentation of this case. The pulmonary veins may have been the seat of lesions causing secondary thrombosis and, consequently, arterial embolism later. It is, however, somewhat difficult to understand how

this thrombosis could have been present in the pulmonary veins since the first occlusion of the arteries of the arm without giving any symptoms, and it is still harder to understand that it could have been present at the time of the onset of hemiplegia three years earlier. The possibility remains that the first arterial occlusion in the arm was due to primary thrombosis and that thrombosis then occurred independently in the pulmonary veins.

It is clear that the episodes of thrombosis occurred in the veins of the general circulation during the patient's last days. The fact that there was hemorrhagic infarction of the lower lobe of the left lung means that an embolus must have been present in the veins of the general circulation, because the foramen ovale was found to be closed. Together with the puerperal thrombosis of the femoral vein and the thrombosis of the pulmonary veins, this constitutes the third localization of venous thrombosis in one patient over a period of years. Within the same space of time episodes of acute arterial occlusion appeared, of which the one resulting in hemiplegia is most reasonably assumed to have been caused by thrombosis in situ.

Without a complete microscopic study of all the vessels and without positive findings of changes in the coagulability of the blood, we have felt it warranted to include this case in the group of cases of thrombosing disease because of the similarities in the clinical pictures. In addition, the pathologic picture did not suggest the typical picture of the known forms of arteritis or degenerative lesions of the arteries.

GENERAL COMMENT

Five cases of occlusive arterial disease which resulted in gangrene have been reported. Four of the patients (cases 1 to 4) were seen at the clinic in the last two or three years, and the fifth patient was seen at the clinic in 1924. Of a large series of cases of vascular disease studied during these years, these five cases have been regarded from the clinical point of view as irregular, in that the condition could not be considered as fulfilling the requirements of the hitherto well known groups of arterial occlusive disease either with regard to the clinical history and objective physical findings or the pathologic characteristics of the occluded vessels. These cases most likely have to be considered under the rather poorly defined term simple thrombosis. The group of conditions represented by the term simple thrombosis, however, may be said at the present to comprise so many various clinical conditions that it would be warranted, in the absence of definite knowledge as to their pathogenesis and etiology, to attempt segregation into the various groups of simple thromboses mainly on the basis of the clinical picture. In the present cases such an attempt seems all the more justifiable because of

certain characteristic features of changes in the coagulability of the plasma, a finding which also introduces the possibility for a discussion of the etiology of the pathologic process.

Four of the five patients were men, and all five were gentiles, their ages ranging from 26 to 53 years. In only one of these cases could the pathologic changes be considered to be secondary to operation. In case 2 there was the characteristic picture of chronic infectious arthritis, which, however, had not been active for seven or eight years preceding the onset of the vascular disease and for this reason was not considered as an etiologic factor. In the other cases the possibility of infection was excluded. As to the presence of an underlying primary disease, none was found. In case 3 the possibility of the existence of such an underlying primary disease was not entirely excluded, as was pointed out in the discussion of the differential diagnosis, although such a possibility seems somewhat remote. We have therefore considered the process to be of a primary or essential nature.

The clinical picture is characterized by recurrent episodes of acute arterial occlusion in the large and the small arteries of the extremities as well as in those of the brain. The episodes may subside after a few hours or a few days, with complete recovery; on the other hand, occlusion may frequently lead to gangrene and to subsequent amputation of a small or large part of the involved extremity. In cases 1 to 3 the patient suffered an acute attack while going about his work and feeling perfectly well. In cases 4 and 5 the attack was just as acute, even though the patient had suffered previous occlusion of an artery of the brain. Frequently, an episode of arterial occlusion is preceded by, associated with, or followed by, one or several episodes of localized or migrating thrombosis in the superficial or deep veins. The subjective symptoms are those characteristic of any vascular occlusion, as are also the objective findings. Otherwise the general physical examination has been unimportant. The systemic reaction is characterized by low grade fever or by a completely afebrile condition, with or without leukocytosis. The other routine laboratory examinations are of no essential interest. Microscopic study of the vessels involved indicated a nondegenerating noninflammatory reaction, with slight cellular reaction in the wall of the vessel, including the adventitia, as seen in cases of simple thrombosis.

The diagnosis of the condition is reached by excluding the presence of a degenerative arterial lesion. Thrombo-angiitis obliterans is ruled out mainly by the absence of persistent symptoms, subjective or objective, of arterial insufficiency before the acute onset, by the objective findings of normally open vessels, except the ones occluded after the onset, and by the absence of the chronic inflammatory character of the occlusion as seen under the microscope in the typical case of thrombo-

angiitis obliterans. Sterile blood cultures and the absence of inflammatory reaction exclude arteritis of specific or nonspecific origin. Exclusion of the embolic factor in the occlusion is the most difficult problem in this group of cases, and it can be achieved only after the most careful physical examination. The occurrence of venous thrombosis is of material assistance in the process of differentiation.

Since it has seemed to us sufficiently evident that we are probably here dealing with a definite clinical entity, we have called it by a purely descriptive term, the thrombosing disease, or essential thrombophilia, and the establishment of the clinical picture has been the main purpose of this paper. The clinical investigation in these cases has been accompanied with special examination of the coagulability of the plasma, according to a method previously reported. One of the patients (case 5) was seen several years before such hematologic investigations were employed, and no information is at hand to indicate whether or not changes in coagulability were present. In the other four cases a moderate to marked increase in the coagulability of the plasma was found. In two of the cases in which the patients were followed through several episodes of the thrombosing tendency (cases 1 and 2) the active episodes of thrombosis were accompanied with coinciding episodes of increasing coagulability of the plasma. The possibility that these hematologic findings were the result of hematologic reactions to the already formed thrombus has been seriously considered; however, this possibility seems justly to be ruled out by control observations in some fifty cases of arteriosclerosis obliterans and thrombo-angiitis obliterans in which no such changes were observed. In a large number of observations of patients who have undergone surgical operations of one kind or another similar changes of increasing coagulability of the plasma have been recorded in a high percentage of cases in which there was the complication of postoperative thrombosis or embolism. These observations led to the assumption that, so far as can be seen, the changes in coagulability in cases of essential thrombophilia are not to be considered as specific for this disease. It is even possible, as will be discussed later, that these changes are not altogether necessary requirements for the diagnosis of essential thrombophilia. In four of the cases reported, however, this change in coagulability was present.

From an etiologic point of view this strongly suggests to us the probability that the thrombosing episodes stand in some etiologic relationship to the episodes of hematologic changes, as recorded by our method of investigation of the coagulability of the plasma. To prevent misunderstanding and misinterpretation we wish to emphasize the point that this does not mean that thrombosis occurs because the blood clots in the vessels. It has been shown and repeatedly emphasized by

Aschoff [4] that thrombus formation in vivo is not one of coagulation of the blood but an entirely different process. Without going into a detailed discussion of the process, it may be of interest to point out a few outstanding facts as a basis for our etiologic consideration: Morphologically, one part of the thrombus is white; it is called the head of the thrombus and is the first part formed. It is made up of a characteristic network or by the formation of lamellae, consisting of only a little fibrin but a great abundance of platelets, laid down not in the stagnated but in the streaming blood of a certain velocity. The primary question then arises: How are the platelets precipitated or agglutinated to form the first nucleus of the thrombus? A discussion of this point involves important problems of a physical, colloidal and chemical nature. It may briefly be stated that the blood can be considered as a colloidal system in which are suspended the corpuscular elements of the blood. The first process in the formation of a thrombus is a loss of suspension stability of the platelets. Theoretically this may be caused by changes in the intimal lining of the vessel, in the velocity of the blood stream or in the blood platelets themselves. In our group of cases we have found a strong indication of the presence of certain hematologic changes. It is therefore only natural that this is influencing our line of thought and that we tend to consider the changes in the platelets themselves as being of primary importance. The suspension stability of the corpuscular elements of the blood is affected by the physicochemical nature of the plasma, and this interrelation of the corpuscular suspension stability and the nature of the colloidal blood plasma has been shown by Fåhraeus [5] for the red corpuscles to be due mainly to the qualitative and quantitative condition of the serum proteins. Starlinger [6] has pointed out that an increase in the globulin-fibrinogen fraction reduces the suspension stability of the platelets and thereby favors the occurrence of thrombus formation.

We have entered into this somewhat detailed discussion in order to reach this very point, where the value and limitation of our testing of the coagulability of the plasma may most properly be discussed. In two of our cases (cases 1 and 2) is reported a marked increase in the globulin-fibrinogen fraction of the serum proteins. In case 1 this seems to have been markedly pronounced, with a return to normal on the first visit of the patient six months after his first dismissal. We have no

4. Aschoff, Ludwig: Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924.

5. Fåhraeus, Robin: The Suspension Stability of the Blood, Physiol. Rev. **9**:241-274 (April) 1929.

6. Starlinger, Wilhelm: Ueber die klinische Bedeutung des physikochemischen Zustandes der zirkulierenden Eiweisskörper des Blutes und Gewebes, Zentralbl. f. inn. Med. **48**:418-431 (April 23) 1927.

simultaneous determinations of the suspension stability or the agglutinability of the platelets and the coagulability of the plasma; therefore, it remains to be seen whether or not impaired suspension stability and increased coagulability are two aspects of the same factor. With this question unanswered, the possibility remains that changes in the coagulability of the plasma may not be an absolute requisite for essential thrombophilia. But with the finding of an increased coagulability of the plasma in four of our cases, it is strongly suggested that the primary hematologic change in this condition is due to the physicochemical nature of the plasma. Our qualitative and quantitative determinations of the serum protein content indicate that an increased globulin-fibrinogen fraction may be responsible; that, however, can only partly explain the process, as no direct parallel between the globulin-fibrinogen fraction and the coagulability can be found. Other principles in the plasma, either of a chemical or of a physical nature, must be involved, as is also easily deduced from conditions of hemorrhagic tendency in hemophilia and obstructive jaundice in which the marked change in coagulability is not found to coincide with any qualitative or quantitative laboratory method as yet employed. For this reason it remains entirely futile to attempt to theorize as to the primary nature of the changes leading to these hematologic abnormalities in the cases reported here. For the same reason we have not found any specific treatment for the disease.

SUMMARY

Five cases are presented in detail, in all of which there was thrombosis of the larger arteries and veins, not only of the extremities but also of other regions of the body. This thrombosing disease shows a tendency toward relapse, with recurrence of thrombosis. The thrombosis is initiated without evidence of antecedent disease or of existing disease or any known predisposing factors. The pathologic changes in the vessels are those of a nonreacting type of thrombosis without evidence of disease in the intima or other coats of the vessel. There is an associated hypercoagulability of the plasma during these episodes. It is believed that this condition represents a separate disease entity, and to it has been given the name essential thrombophilia.

REVERSIBLE AUTOHEMAGGLUTINATION WITH PERIPHERAL VASCULAR SYMPTOMS

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Prior to the beginning of the twentieth century transfusion was a dangerous procedure, usually being followed by violent and often fatal reactions. In 1900 Landsteiner [1] discovered the cause for these reactions, namely, the presence in the human serum of agglutinins which when mixed with sensitive cells cause marked agglutination. These are called iso-agglutinins because of their specific action on cells from the blood of a subject of the same species and must be differentiated from hetero-agglutinins, which produce similar reactions between the bloods of subjects of different species. On the basis of these iso-agglutinins the four blood groups are distinguished.

Certain errors in determining blood groups occasionally have arisen because of pseudo-agglutination or excessive rouleaux formation (Shattock,[2] 1900). This condition is common in cases of acute infection and is apparently due to increased viscosity of the serum. Marked rouleaux formation may cause clumping which simulates true agglutination. Slight dilution (1:3) dissipates pseudo-agglutination, so that it can be readily distinguished from iso-agglutination, which usually has a high titer.

Another source of error sometimes observed in grouping bloods is that due to cold agglutinins, which are so called because of their action only at low temperatures. The action is nonspecific, in that the serum will agglutinate the cells from blood of all groups and even the patient's own blood. A certain amount of confusion has arisen in the literature because of the names used to designate the phenomenon of cold agglutination: auto-agglutination, autohemagglutination and panagglutination. All these terms have also been used at one time or another to describe rouleaux formation.

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1. Landsteiner, K.: Zur Kenntnis der antifermentativen, lytischen und agglutinierenden Wirkungen des Blutserums und der Lymphe, Centralbl. f. Bakt. (Abt. 1) **27**:357 (March) 1900.

2. Shattock, S. G.: Chromocyte Clumping in Acute Pneumonia and Certain Other Diseases and the Significance of the Buffy Coat in the Shed Blood, J. Path. & Bact. **6**:303, 1900.

Cold agglutination, although probably observed by earlier workers, was first clearly described by Landsteiner [3] in 1903, who noted its occurrence in animals. Many other descriptions of cold agglutinins in animals may be found. Table 1 differentiates types of agglutination.[4]

Christy [5] reported the frequent occurrence of agglutination in trypanosomiasis in man. Details, however, are lacking to establish the true nature of this agglutination.

The first definite cases of cold agglutination noted in human beings were those reported by Clough and Richter [6] in 1918. In 1931 Boxwell and Bigger [7] were able to collect reports of only twenty-two cases which satisfied their definition: "Autohemagglutination is a clumping of the erythrocytes into irregular masses, visible to the naked eye, occurring in the presence of the subject's own serum, without bacterial action, at air temperature and reversible at body temperature." The instances

TABLE 1.—*Differentiation of Pseudo-Agglutination, Cold Agglutination and Iso-Agglutination (After Landsteiner [4])*

	Pseudo-Agglutination	Cold and Auto-Agglutination	Iso-Agglutination
Absorption of active principle	Not absorbable	Absorbable	Absorbable
Effect of temperature on tests	Not weaker; rather stronger at 37 C. than at lower temperatures	Occurs as a rule only at low temperatures	Little affected by changes of temperature from 0 to 37 C.
Effect of dilution	Inactivated by slight dilution	Stands considerable dilution	Stands considerable dilution
Specificity	Nonspecific	As a rule nonspecific	Group specific

which satisfied this definition were noted under a variety of conditions, eight being in females and fourteen in males. Five of the subjects were in normal health, and five suffered from diverse conditions, such as bronchopneumonia, secondary anemia, pernicious anemia, hypersensitiveness and unspecified anemia. In the remaining twelve cases there was some interference with the function of the liver, as shown by jaundice and enlargement of the liver. In eight cases the spleen also was reported

3. Landsteiner, K.: Ueber Beziehungen zwischen dem Blutserum und den Körperzellen, München. med. Wchnschr. **50**:1812 (Oct. 20) 1903.

4. This table is adapted from that of Landsteiner cited by A. S. Wiener (Blood Groups and Blood Transfusion, Springfield, Ill., Charles C. Thomas, Publisher, 1935).

5. Christy, C.: Sleeping Sickness (Trypanosomiasis), Brit. M. J. **2**:1456 (Nov. 26) 1904.

6. Clough, M. C., and Richter, I. M.: A Study of an Autoagglutinin Occurring in a Human Serum, Bull. Johns Hopkins Hosp. **29**:86 (April) 1918.

7. Boxwell, W., and Bigger, J. W.: Autohemagglutination, J. Path. & Bact. **34**:407 (July) 1931.

to be enlarged. In eleven of the twenty-two cases anemia was a definite feature of the illness. Four of the patients had syphilis. Three instances of familial occurrence were noted.

In addition to the cases reported by Boxwell and Bigger we have been able to find reports of twenty-four cases in which the authors said they considered that auto-agglutination was manifest. Only fifteen of these reports presented sufficient data so that the condition may be considered as true autohemagglutination.

Cases which cannot be accepted as instances of true autohemagglutination were reported by Reimann,[8] Foord[9] (4 cases), Thiodet and Ribère,[10] Benhamou and Nouchy[11] and Foord and Randall.[12] The patients reported on by Reimann, Foord and Foord and Randall all had multiple myelomas with hyperproteinemia. All of these obviously were cases of pseudo-agglutination. Benhamou and Nouchy's case cannot be considered as one of true autohemagglutination, as the serum was shown not to contain any abnormal agglutinins; rather the cells agglutinated when mixed with serum of another subject of the same blood group (Thomsen phenomenon?). The agglutination persisted at 37 C. but disappeared at from 40 to 45 C. Thiodet and Ribère's case probably was one of pseudo-agglutination, as the reaction was not reversible at a temperature of 56 C. for one-half hour and agglutination was not noted on dilution.

To the list of cases of true autohemagglutination we wish to add a case from the Indiana University Medical Center which is interesting in that all the symptoms can be explained by the agglutinative phenomenon. Despite a thorough search for a possible etiologic factor, none could be found, and after treatment marked symptomatic improvement was noted.

C. S., a white man aged 57 years, was admitted to the medical service of the Indiana University Hospitals on Nov. 6, 1935, complaining of bluish dis-

8. Reimann, H. A.: Hyperproteinemia as a Cause of Autohemagglutination: Observations in a Case of Myeloma, J. A. M. A. **99**:1411 (Oct. 22) 1932.

9. Foord, A. G.: Hyperproteinemia, Autohemagglutination, Renal Insufficiency and Abnormal Bleeding in Multiple Myeloma, Ann. Int. Med. **8**:1071 (March) 1935.

10. Thiodet and Ribère: Grande auto-agglutination des hématies, Compt. rend. Soc. de biol. **116**:1389 (June 28) 1934.

11. Benhamou, E., and Nouchy, A.: Grande auto-agglutination des hématies précédée et suivie de grande auto-agglutination des plaquettes, Presse méd. **41**: 25 (Jan. 7) 1933.

12. Foord, A. G., and Randall, L.: Hyperproteinemia, Autohemagglutination and Renal Insufficiency in Multiple Myeloma, Am. J. Clin. Path. **5**:532 (Nov.) 1935.

TABLE 2.—*Cases of True Autohemagglutination* *

Case	Author	Sex	Clinical Notes
1	Clough and Richter [6]	F	Bronchopneumonia
2	Clough and Richter [6]	F	Normal (daughter of patient in case 1)
3	Kliger, I. J.: J. A. M. A. **78**: 1195, 1922	F	Secondary anemia; pregnancy
4	Guthrie, C. G., and Huck, J. G.: Bull. Johns Hopkins Hosp. **34**: 80, 1923	F	Normal
5	Guthrie and Huck	F	Normal (sister of patient in case 4)
6	Guthrie and Huck	M	Normal (brother of patient in cases 4 and 5)
7	Debenedetti, V.: Policlinico (sez. med.) **31**: 311, 1924	F	Anemia; hemolytic jaundice, with enlarged spleen
8	Cohen, H., and Jones, A. R.: Lancet **2**: 853, 1924	M	Pernicious anemia; syphilis
9	Alexander and Thompson [15]	M	Leukemia (myelogenous?); anemia; enlarged spleen; jaundice
10	Greppi, E.: Policlinico (sez. med.) **32**: 61, 1925	M	Hypertrophic infective hepatitis; anemia
11	Greppi	M	Hypertrophic infective hepatitis; anemia
12	Li-Chen-Pien: J. Immunol. **11**: 297, 1926	M	Syphilis; cirrhosis of liver
13	Wyschegorodzewa, W. D.: Ztschr. f. klin. Med. **104**: 524, 1926	M	Jaundice; liver enlarged; syphilis
14	Greppi, E.: Riforma med. **45**: 1374, 1929	M	Splenomegalic hypertrophic hepatitis; anemia
15	Debenedetti, E.: Presse méd. **37**: 1688, 1929	M	Hypersensitiveness (asthma, urticaria, etc.)
16	Debenedetti	M	Hemolytic jaundice; enlarged spleen and liver
17	Debenedetti	F	Normal sister of patient in case 16
18	Lloyd, R. B., and Chandra, S. N.: Indian M. Gaz. **65**: 1, 1930	F	Anemia; spleen enlarged
19	d'Antona, L.: Rinasc. med. **7**: 184, 1930	M	Anemia of chlorotic type; hepatocholangeitis
20	d'Antona	M	Splenohepatic syphilis; anemia; jaundice; spleen and liver enlarged
21	d'Antona	M	Aplastic anemia; spleen and liver enlarged
22	d'Antona	M	Jaundice; spleen and liver enlarged
23	Boxwell and Bigger [7]	F	Anemia and atypical leukemia
24	Iwai and Mei-Sai [16a]	M	Raynaud's disease
25	Iwai and Mei-Sai [16b]	F	Raynaud's disease
26	van der Hoeden, J., and Verbeek, A. G. M.: Nederl. tijdschr. v. geneesk. **75**: 4767, 1931	M	Hypertrophic hepatic cirrhosis
27	van der Hoeden and Verbeek	M	Hypertrophic hepatic cirrhosis
28	van der Hoeden and Verbeek	M	Hypertrophic hepatic cirrhosis
29	van der Hoeden and Verbeek	F	Hypertrophic hepatic cirrhosis
30	Brulé, M.; Hillemand, P., and Bonnard: Bull. et mém. Soc. méd. d. hôp. de Paris **49**: 429, 1933	M	Cirrhosis of liver
31	Manheims, P. J., and Brunner, E. K.: J. A. M. A. **101**: 207, 1933	F	Myelogenous leukemia; anemia
32	LeGoff [17]	M	Raynaud's disease
33	Gonzáles Guzmán, I.: Arch. latino am. de cardiol. y hemat. **3**: 25, 1932	M	Syphilitic aortitis; splenomegaly; intestinal amebiasis
34	Sherman, I.: Am. J. M. Sc. **188**: 487, 1934	F	Lobar pneumonia
35	Sherman	F	Staphylococcic septicemia
36	Sherman	F	Influenzal pneumonia; diabetes mellitus
37	Roth [18]	M	Paroxysmal hemoglobinuria with vasomotor symptoms
38	Belk, W. P.: J. Lab. & Clin. Med. **21**: 697, 1936	F	Lobar pneumonia

* Cases 1 to 23 are reported on by Boxwell and Bigger.[7]

coloration of the fingers, hands, toes, feet, nose, ears and tip of the tongue when exposed to cold air. At times after he had been exposed to cold the urine became red.

The patient had been in excellent health until October 1932 (three years before entry), when, while on a hunting trip, he noticed a red discoloration of the urine. During the winter of 1932-1933 he noticed a recurrence of reddish urine every time he was exposed to cold weather. At that time there were no other symptoms. During warm weather the urine remained normal in appearance. The next winter (1933-1934) the urine was again red, and the patient began to have bluish or purplish discoloration of the distal portion of all the extremities and of the nose and ears when exposed. The same sort of discoloration was noted also on the tip of the tongue after he ate ice-cream. With the discoloration there was no pain or other subjective symptoms except cold, numbness and tingling of the affected part. The bluish discoloration and numbness due to exposure to cold cleared up within five minutes after the application of heat. The urine also became clear in a short time. A year before the patient's admission to the hospital (November 1934), while making a mold and working with cold sand, his fingers became cold. The index finger of the right hand and the middle finger of the left hand became numb and black. The ends of both fingers sloughed, leaving a scar.

With the recurrence of these same symptoms in the fall of 1935 the patient was referred to the hospital for study.

His occupation was that of a molder of metals, largely aluminum, and he came into contact with metallic fumes of brass and aluminum. There had been no one with a similar disorder near him or in his factory.

There were no other complaints except of poor teeth and a rupture, for which he had worn a truss for many years. The patient had always been in robust health. He had gonorrhea in 1905 but said that he had never had syphilis. He had never had malaria. There was no history of other infectious diseases, operations or accidents. He was married, and his wife and three children (aged 31, 29 and 26) were all living and well. His father died of Bright's disease at the age of 69. His mother died at the age of 53 of typhoid. Four brothers and three sisters were living and well. Two other brothers had died—one of heart disease and the other of an unknown cause. No relative had ever complained of symptoms similar to his.

The patient was somewhat obese—height, 5 feet and 7 inches (170 cm.); weight, 189 pounds (86 Kg.). He appeared to be in excellent health. His face was ruddy. He had several carious teeth and enlarged tonsils. The pupils were round and of equal size and reacted to light and in accommodation. Ophthalmoscopic examination revealed no abnormality. The chest was emphysematous, but the lungs were normal. The heart showed no enlargement to percussion, the rhythm was regular, the sounds were distant and a systolic murmur could be heard at the apex. The blood pressure was 135 systolic and 90 diastolic. There was an indirect inguinal hernia on the right of moderate size which was easily reduced. The liver and spleen could not be palpated. The right index finger and the left middle finger were scarred at the tip and shortened by ½ inch (1.5 cm.). The peripheral vessels showed moderate arteriosclerosis. The radial, posterior tibial and dorsalis pedis arteries had normal pulsations. There was a decrease in the ability to feel heat in the distal portions of the extremities. Cold was recognized more readily. The vibratory sense was normal. There was a mottled bluish discoloration of the feet and hands (temperature of the room, 21 C.), which was replaced by mild hyperemia when heat was applied.

The admitting diagnosis was atypical Raynaud's disease, with paroxysmal hemoglobinuria, dental caries, hypertrophied tonsils and indirect inguinal hernia on the right.

Several attempts to make a count of the red blood cells were unsuccessful because of marked clumping of the cells in the diluting pipets. The hemoglobin value ranged between 10.5 and 11.5 Gm. The white blood cell count at the time of the patient's admission to the hospital was 12,200. A differential count showed: polymorphonuclears, 65 per cent; lymphocytes, 19 per cent; metamyelocytes, 8 per cent; band cells, 6 per cent; myelocytes, 1 per cent; basophils, 1 per cent and reticulocytes, 1.6 per cent. The urine was red, acid and cloudy, with a specific gravity of 1.022. Albumin was present (0.083 per cent). Blood was present as determined by the benzidine reaction. There were no red blood cells or pus cells. Subsequent examinations failed to show blood or albumin. The function of the kidneys, as determined by the phenolsulfonthalein tests, was 70 per cent for the first hour and 10 per cent for the second. The Wassermann, Kahn and Kline tests of the blood for syphilis were negative. The basal metabolic rate was normal on two occasions (minus 7 and plus 5). The examination of the spinal fluid, including a Wassermann test and a gold curve test, gave normal results. The sedimentation rate of the blood was 6 mm. in one hour. The cholesterol content of the blood was 237 and 183 mg. per hundred cubic centimeters, respectively, on two occasions. The van den Bergh test showed a slightly delayed reaction. There was 0.57 mg. of bilirubin per hundred cubic centimeters. The icteric index was 5. The galactose tolerance test of the hepatic function revealed no abnormality. The Takata-Ara reaction was negative. Chemical analysis of the serum showed 7.4 Gm. of protein, 4.2 mg. of phosphorus and 10.3 mg. of calcium per hundred cubic centimeters. The fragility of the red blood cells was within normal limits (initial hemolysis, 0.46; complete hemolysis, 0.32). The Donath-Landsteiner reaction showed no hemolysis on chilling.

No trypanosomes were present in blood smears or in the blood of a rat, a mouse or a guinea-pig five days after inoculation with the blood of the patient.

Roentgenograms of the chest showed mild cardiac enlargement, considerable prominence of the left auricular node and mild congestive changes in both pulmonary fields.

During the patient's stay in the hospital the temperature remained consistently below the normal line, averaging 97.6 F. (36.4 C.) and ranging from 96 to 99 F. (35.6 to 37.2 C.).

The clumping of the blood in the diluting pipets suggested autohemagglutination; so the count was again attempted with the pipets, solutions and microscope under the rays of a heat lamp at a temperature of 37 C. In this manner counts were made without difficulty. The red blood cells numbered 3,040,000 and the platelets 203,680. No great difficulty was encountered in making satisfactory blood smears at room temperature.

Ten cubic centimeters of the blood of the patient together with 1 cc. of a 2.5 per cent solution of sodium citrate was centrifugated at body temperature, and the cells were washed in physiologic solution of sodium chloride. The cells were used to determine the blood type, and the blood was found to belong to group A (type II). At room temperature (25 C.) the patient's serum agglutinated the cells from all four groups with equal rapidity.

Various dilutions of the serum were made, and 1 drop of a suspension of the cells which had been separated and washed was added to each dilution. Agglutination was noted grossly and microscopically to a dilution of 1:1,024 after

thirty minutes of chilling at 10 C. Agglutination disappeared in all dilutions after five minutes in the incubator at 37 C. At 15 C. the titer was noted as 1:64, and at 27 C., as 1:8 (table 3).

An experiment was performed to determine the temperature of the skin of the feet under various conditions. The temperature was measured with the thermocouple (dermotherm) with the patient in a recumbent position. The temperature of the knees, calves, ankles, dorsum of each foot and toes was measured at room heat (25.6 C). A photograph taken at that time shows the normal appearance of the skin (fig. *A*). The room temperature was then lowered to 20 C. After a few minutes the changes previously described; i. e., mottling, bluish discoloration, with slight numbness, began to appear and were well marked in fifteen minutes, at which time a second photograph was taken (fig. *B*). The

TABLE 3.—*Agglutination of the Patient's Cells by His Own Serum*

Titer	1:1	1:2	1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:512	1:1,024
10 C.	++++	++++	++++	++++	++++	++++	++++	++++	++++	+++	+
15 C.	++++	++++	++++	++++	++++	++++	+++	++	0	0	0
27 C.	++++	++++	++++	++	0	0	0	0	0	0	0
37 C.	0	0	0	0	0	0	0	0	0	0	0

TABLE 4.—*Temperatures of the Skin in Degrees Centigrade*

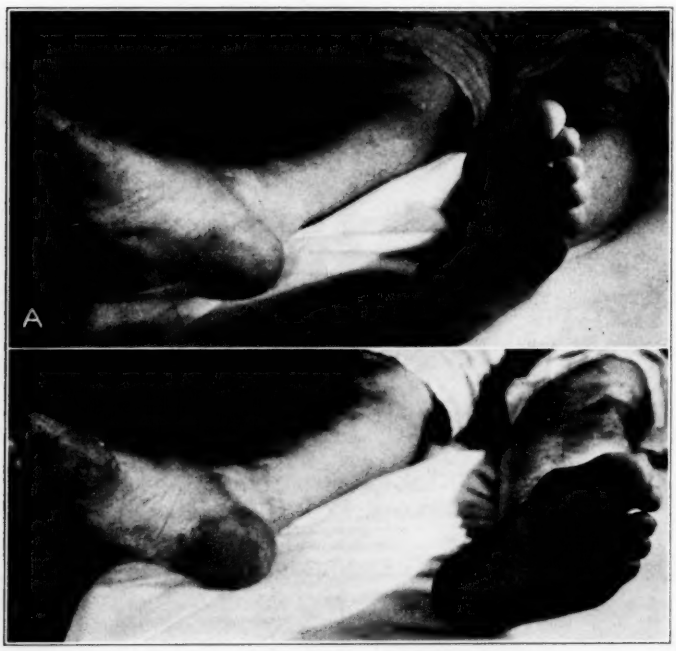
Location		Room at Temperature of 25.6 C.	Room at Temperature of 20 C.	After Immersion of Arms at 43.3 C. for 20 Minutes
Knee	Right	31.6	30.1	30.2
	Left	31.3	29.8	30.1
Calf	Right	31.4	29.9	30.1
	Left	31.0	29.5	30.0
Ankle	Right	29.0	26.0	25.7
	Left	29.0	25.5	25.2
Dorsum of Foot	Right	29.9	27.2	26.6
	Left	29.4	26.6	26.6
Great Toe (Dorsum)	Right	29.1	23.6	23.5
	Left	28.0	23.0	23.2
Little Toe	Right	26.7	22.6	22.7
	Left	26.5	22.2	22.6

surface temperatures were again measured. The patient was asked to immerse both arms to a point above the elbows in water at 43.3 C., and the temperatures were again read after twenty minutes of immersion. The results are shown in table 4.

Normally, according to Landis and Gibbon,[13] a response—an increase in the surface temperature of the foot—is noted within fifteen minutes after immersion of the forearms in water at 43 C., and in all normal subjects the temperature reaches at least 31.5 C. within twenty-nine minutes. Any failure to show this rise is indicative of occlusive vascular disease. There was no appreciable change in the temperature in our case twenty or thirty minutes after immersion.

13. Landis, E. M., and Gibbon, J. H., Jr.: Simple Method of Producing Vasodilatation in the Lower Extremities with Reference to Its Usefulness in Studies of Peripheral Vascular Disease, Arch. Int. Med. **52**:785 (Nov.) 1933.

On two occasions the patient was asked to expose himself dressed only in street clothes to an outdoor temperature of about 0 C. Both times he complained in about ten minutes of numbness of the hands, feet, nose and ears. Each of these members was dark purple and felt cold to touch. Room temperature restored the normal healthy color within ten minutes, the change being rapid from purple to gray to an erythematous hue (with splotchy white patches) to normal pink. Sensation returned to normal at the same time. Examination of all the specimens of urine for several hours afterward showed no trace of blood with the benzidine reaction.



A, photograph of the lower extremities at room temperature; *B*, fifteen minutes after the temperature was lowered to 20 C.

In an attempt to produce the phenomenon by local chilling, both arms were immersed in water at 4.4 C. for five minutes. The changes noted were not those expected, being an extreme blanching of the skin in all immersed areas and a feeling of numbness, cold and tingling. A normal color soon returned when the arms were exposed to room temperature. Specimens of urine did not contain blood.

As the moderate degree of anemia seemed to be the only finding of importance, and since many of the patients with autohemagglutination reported on in the literature had this condition, the patient was given iron (3 pills of ferrous

carbonate three times a day) and liver extract.[14] For empirical reasons he was also given theobromine, 15 grains (1 Gm.) three times a day. Under this therapy he was discharged on December 19.

As he lived near the hospital, he reported from time to time that he was markedly improved and had been able to return to work. He was next seen in the hospital on Feb. 28, 1936, when he came in for a check-up examination. At that time he stated that the symptoms noted during the past four winters had nearly disappeared, and he attributed his improvement to the therapy. Blueness of the nose and ears had been noted on only three or four occasions. He had been outdoors, well clothed, on one occasion when the temperature was —14 F. (—25.5 C.) without discomfort. The return of symptoms had been noted always on raw, damp days with the temperature above freezing. Hemoglobinuria was noted only twice, each time after a short exposure without proper protection on damp days. The results of physical examination were essentially the same as previously. Owing to the fact that he had a job to maintain, the patient stayed in the hospital only overnight. His temperature at 8 p. m. and 8 a. m. was recorded as 98 F. (36.6 C.). Clumping of the blood in diluting pipets was again noted unless the solutions were warmed. A blood count showed: hemoglobin, 11 Gm.; red cells, 3,120,000, and white cells, 6,700, with a normal differential count. The urine was normal and showed a negative test for blood. The cholesterol content of the blood was 176 mg. per hundred cubic centimeters. Agglutination tests again were made and showed practically no change, except that agglutination was noted to a titer of only 1:512 at icebox temperature, instead of 1:1,024.

COMMENT

The significance of the laboratory and experimental work is apparent. The man was in good health except for a peculiar condition of the blood, which caused some suffering and inconvenience during the winter months. His financial condition and family ties made it impossible for him to move to a warmer climate. The cause of autohemagglutination was not determined, although a careful search for an organic origin was made. The history suggestive of paroxysmal hemoglobinuria could not be substantiated by frequent examinations of the urine for blood. All the tests showed negative results except the one at the time when the patient was first admitted to the hospital. The Donath-Landsteiner test for cold hemolysins also was negative.

Only five cases are recorded in which the patient showed symptoms of a peripheral vascular nature (Alexander and Thompson,[15] Iwai and Mei-Sai [16] [two cases], LeGoff [17] and Roth [18]). Each patient presented

14. The preparation used was extralin, 3 capsules three times a day.

15. Alexander, H. L., and Thompson, L. D.: Autohemagglutination in Chronic Leukemia, J. A. M. A. **85**:1707 (Nov. 28) 1925.

16. Iwai, S., and Mei-Sai, N.: (*a*) Etiology of Raynaud's Disease: Preliminary Report, Japan M. World **5**:119 (May) 1925; (*b*) Etiology of Raynaud's Disease, ibid. **6**:345 (Dec.) 1926.

17. LeGoff, J. M.: Sur la forte auto-agglutinine du sang dans certaines maladies périphériques, Presse méd. **41**:628 (April 19) 1933.

18. Roth, G.: Paroxysmal Hemoglobinuria with Vasomotor and Agglutinative Features, Proc. Staff Meet., Mayo Clin. **10**:609 (Sept. 25) 1935.

blueness of the peripheral parts and numbness on exposure to cold, the symptoms remitting when the parts were warmed, as in our case. Iwai and Mei-Sai and LeGoff went so far as to advance the hypothesis of autohemagglutination as a cause of Raynaud's disease. LeGoff's patient showed sloughs from the lower extremities. Clough and Richter [6] recognized the danger of intravascular agglutination, and the Japanese authors Iwai and Mei-Sai demonstrated the possibility of intracapillary agglutination in vitro, using glass tubes and passing blood through at various temperatures. They observed also what appeared to be clumping in the conjunctival capillaries after chilling by using a corneal microscope.

The theory of intravascular plugging by agglutinated cells seems perfectly plausible and would explain all the symptoms in our case. Vascular occlusion was shown to be present by testing the temperature of the skin. Since the reaction was completely and immediately reversible at internal body heat, embolic phenomena did not occur. The symptomatic improvement noted in our case without a change in climate, without any appreciable change in the blood count and without much lowering of the titer of the agglutinin might be explained by the vasodilating action of theobromine, which was sufficient to maintain adequate circulation even when agglutination did occur. Of course, spontaneous remission must be considered. Liver therapy seemed to be of little value, and this was discontinued shortly after the patient's second admission to the hospital.

The apparent confusion in the literature regarding the term autohemagglutination suggests that a more descriptive term for the condition described by Landsteiner and Boxwell and Bigger is needed. We submit that *reversible autohemagglutination* fully conveys the meaning desired and will prevent any confusion with pseudo-agglutination, iso-agglutination, panagglutination and the many other similar terms sometimes used.

In connection with this condition it is interesting to note that, in spite of the difficulty in typing and cross-matching, only one instance of an incompatible transfusion is recorded (Alexander and Thompson [15]). How many cases of this type have not been reported in the literature?

Dr. C. G. Culbertson, director of the laboratory of the Indiana University Hospitals, informed us that he knew of several cases in which cold agglutinins confused the technicians while typing and cross-matching the blood of donors. Unfortunately no record of these has been kept, but no difficulty in making the transfusions has been noted. The technic in our laboratory includes warming the blood to 37 C. when there is any abnormality, in order to rule out cold agglutinins (reversible autohemagglutination).

It is possible that reversible autohemagglutination occurs more frequently than the literature indicates but is not observed because the test

is not made. It is also entirely possible that some atypical peripheral vascular conditions may be explained wholly or in part by the condition of reversible autohemagglutination.

SUMMARY

Autohemagglutination (cold agglutination) is differentiated from iso-agglutination and pseudo-agglutination.

A summary of the literature reveals reports of thirty-eight cases in which sufficient data are presented to confirm a diagnosis of true autohemagglutination.

The report of a case of autohemagglutination is presented in which there were symptoms of peripheral vascular disease and in which improvement followed treatment.

The theory of intravascular plugging with agglutinated cells and the production of symptoms is discussed.

The use of the term *reversible autohemagglutination* is suggested to prevent confusion in the literature.

SALMONELLA SUIPESTIFER INFECTION IN HUMAN BEINGS

REVIEW OF THE LITERATURE AND REPORT OF TWENTY-ONE NEW CASES

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Since the first description of the hog cholera bacillus by Salmon and Smith in 1885, many reports of food poisoning as well as of sporadic infection in human beings due to this organism have appeared. Twenty-one patients with Salmonella suipestifer infection have been treated at the Johns Hopkins Hospital since April 1933. In view of the relative frequency of this infection in Baltimore, it seems desirable to report these cases and to review the literature in order to determine more clearly the clinical manifestations of S. suipestifer infection in man.

In 1902 Longcope published a report of two cases of human infection of a typhoid-like nature with leukopenia caused by a "paracolon" bacillus. Later studies by TenBroeck revealed that the organism isolated by Longcope belonged to the hog cholera bacillus group. Prior to the appearance of this article no infection due to this organism in human beings had been described. Many outbreaks of food poisoning caused by this bacillus have appeared in Europe and Asia, the majority of them occurring during the World War and in the following years. The literature is filled with lengthy discussions as to the pathogenicity of this organism for man. About fifty proved sporadic cases have been described. In this country three outbreaks of food poisoning and eighteen sporadic cases of the infection have occurred, eleven of the patients being admitted to the Johns Hopkins Hospital. The analysis of cases in this report includes fifty cases from the literature of proved S. suipestifer infection and the twenty-one cases of the present series.

DISTRIBUTION

Infection due to this organism has been reported from almost all parts of the world. Outbreaks of food poisoning have been studied in Germany, Switzerland, England, Albania, Turkey, Mesopotamia, Palestine, the West Indies and the United States. The majority of the

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sporadic cases have been reported from Holland, England and the United States.

EPIDEMIC OUTBREAKS DUE TO A KNOWN SOURCE OF INFECTION [1]

The clinical picture is similar in all these cases. After an incubation period varying from three to ninety-four hours, but usually ranging from twelve to twenty-four hours, the patient suddenly becomes ill with headache, fever, abdominal pain, nausea, vomiting and diarrhea and in the cases of more severe involvement with prostration and even stupor. In a few instances chills occur, and some of the children affected have convulsions. In a small percentage of the cases the spleen is palpable, herpes occasionally appears, muscular weakness sometimes supervenes and, rarely, rose spots are present. Pneumonia is a rare complication, and general paresis of the muscles is described. Recovery from the acute symptoms is usually rapid, but complete convalescence may take from seven to ten days. In only five of a total of fourteen hundred and twenty-five cases in which the diagnosis was proved bacteriologically was the illness fatal. The source of infection has varied. Usually meat, such as pork, sausage or ham, is responsible, but such varied agents as tapioca pudding, ice cream, milk, crab-meat and veal have been incriminated. Knorr isolated the organisms from imported Chinese egg yolk but reported no cases of infection. In ten of the twenty epidemics the organism was isolated from the stool, in ten cases from the urine and in two from the blood stream.

SPORADIC CASES

Age, Sex, Race, Seasonal Incidence and Mortality.—The majority of the cases of bacteremia due to S. suipestifer occurred during the first decade of life. Thirty-six of a total of sixty-seven patients, including those of the present series, belonged in this period. In striking contrast to this are the mortality statistics. In the whole series there were twenty-two deaths. Among patients less than 25 years of age the mortality was 19 per cent, while among those over this age it rose to 58 per cent. Of course the number of patients in the latter group was fairly small. The youngest patient on record was 5 weeks of age and the oldest (case 21 of this series) 70 years. Practically every race has been found to be susceptible. Among the patients reported from this hospital there were twenty-seven Negroes and only five white persons. There is no particular seasonal incidence.

1. Bernhardt; Bosch; Clarenburg; Demnitz; Geiger, Greer and White; Griffin; Grüttner; Kauffmann; Kaunitz and Trawińsky; Krumwiede, Provost and Cooper; Lewy and Schiff; Schmidt; Schnitter; Scott; Stewart and Litterer, and Walther.

Uncomplicated Bacteremia—Typhoid-Like Infection.[2]—Forty-four of the seventy-one patients were without localizing signs, eleven of the patients in the present series being of this type. In this group the average age was 13 years, the youngest patient being 7 months and the oldest 55 years of age. The sexes were equally affected, and in only nine cases, or 20 per cent, did the disease prove fatal.

The clinical picture of this type of infection is not unlike that of typhoid, and this diagnosis is often made when the patient is admitted to the hospital. However, in many instances there are features which serve to distinguish it.

The onset is usually sudden, but in from one fourth to one third of the patients the disease begins gradually over a period of two or three days. Fever is the predominant symptom at the onset. A marked degree of pyrexia is noted, the temperature often being 104 or 105 F., but this is not invariably the rule. The duration of the fever varies

TABLE 1.—*The Sporadic Cases: A Comparison of Forty-Six Reported Cases with the Present Series of Twenty-One Cases*

Age, Years	Number of Reported Cases	Number of Fatal Cases Reported	Number of Cases in Present Series	Number of Fatal Cases in Present Series
0- 5	17	3	10	1
5-10	5	0	4	0
10-15	3	1	0	0
15-20	6	3	1	0
20-25	3	2	0	0
25-30	5	2	0	0
30-35	3	3	3	2
35-40	1	1	2	0
Over 40	3	3	1	1
Total	46	18	21	4

considerably, but in the average case it lasts for from two to ten days. Anorexia is almost always a complaint. Vomiting and headache occur with great regularity. A shaking chill at the onset occurs in about 10 per cent of the cases. Dry cough and coryza are frequently noted. Diarrhea was complained of in thirteen of the cases, while constipation was noted in approximately 10 per cent. Worthy of mention is the frequent complaint of abdominal pain. Many of the patients have abdominal distention and tenderness and occasionally a slight degree of muscle spasm. Owing to these signs and symptoms needless operations have been performed. Other symptoms which occur occasionally are convulsions (especially in children), drowsiness, delirium, articular pains without objective findings and pain in the back. A history of epistaxis was noted in three cases.

2. Bauer and McClintock; Boller; Branham, Motyca and Devine; Dijkstra; Haynes and Meiks; Hicks and Robertson; Köbe; Krüger; Kuttner and Zepp; Mackenzie; Matveld; Nabarro, White, Dyke and Scott; Neukirch; Rau and Shaw.

The physical findings are those common to any acute infection with an invasion of the blood stream. Hyperpyrexia, a coated tongue and abdominal distention are almost always present. In contrast to the findings in typhoid, the pulse rate is usually rapid. However, a relative bradycardia is occasionally seen. Meningismus is a common finding in children but is rarely observed in adults. The large majority of children are drowsy, but many of the adult patients look surprisingly alert in the presence of such a high temperature. Herpes rarely occurs. Rose spots almost never are seen. Mild bronchitis is commonly noted in older patients. In a few cases the liver is palpable, and even less frequently there is slight general enlargement of the lymph nodes. In approximately one fifth of the cases the spleen is palpable.

Complications during the course of this infection are rare. Jaundice has been reported in three cases. Two intestinal hemorrhages occurred during the course of a mild typhoid-like infection in a 28 year old Indian reported by Duncan. Although the organism obtained by culture of

TABLE 2.—*The Initial Symptoms in the Twenty-One Cases in the Present Series*

Fever	21	Abdominal pain	5
Vomiting	10	Delirium	5
Cough	7	Drowsiness	4
Coryza	6	Chill	3
Diarrhea	6	Headache	2
Constipation	5	Convulsions	2
Pains in joints	2		

the blood was not entirely typical of S. suipestifer, serum agglutination with stock strains was 1 : 80, while tests with all other antigens showed negative results. Parotitis was a fatal complication in one case. Purpura occasionally developed, and its appearance was always associated with an unfavorable outcome. Culture of the urine in five of these cases gave positive results, but there were no clinical manifestations of urinary infection. In a moderate number of cases a slight degree of anemia developed during the course of the illness, but the blood returned rapidly to normal when the infection subsided. Of interest are the numerous cases in which the condition has developed in persons previously inoculated with typhoid vaccine.

In only an occasional case is the organism observed in the stool. The majority of patients present no recognizable source of the organism in the body, and the manner of its entrance and mode of dissemination are usually entirely unknown.

Cases of Pulmonary Involvement.[3]—Among the pulmonary manifestations which occur during the course of S. suipestifer infection are

3. Bauer and McClintock; Boller; Bullowa; Kuttner and Zepp; Neukirch; van der Hoeden and Hulst, and Weil and Saxl.

bronchopneumonia, occasionally lobar pneumonia, pleurisy with effusion and empyema. Twenty-four, or approximately one third of the seventy-one patients with the diagnosis proved, including the twenty-one in the present series, had definite evidence of pulmonary or pleural involvement. In a large majority bronchopneumonia was noted. The average age of these patients was 19 years. The sexes were about equally affected. Ten of the twenty-four patients died. The symptoms and physical signs were similar to those seen in pneumonia due to other organisms. In one of the cases reported by Kuttner and Zepp in 1933 purpura developed, and the bronchopneumonia was discovered at autopsy to be interstitial. Since purpura is a common finding in pigs infected with the virus of hog cholera, the possibility of such an etiologic relationship was mentioned in this case, but no virus studies were made. No other instances of pneumonia of this type have been noted in cases of S. suipestifer infection.

The temperature is usually high, with a daily variation of from 0.5 to 2 F. In the bronchopneumonic type it comes to normal by slow lysis, but several patients with essentially lobar involvement showed termination by typical crisis. Frequently the pneumonia is bilateral.

In six cases bacteriologic proof of the rôle played by the suipestifer bacillus in these infections has been obtained. Five of these cases were reported in the literature, and one belonged in the present series. In an unusual case of lobar pneumonia the bacillus was recovered from the sputum and from the blood stream (Bullowa). In two cases of the Glässer-Voldagsen type described by Neukirch it was obtained in pure culture from the lung at autopsy. In case 18 of the present series lobar pneumonia with pleural effusion developed during the course of pregnancy, which was already complicated by myocardial insufficiency. Fluid obtained by thoracentesis was sterile, but blood culture revealed a gram-negative rod, and at autopsy S. suipestifer was grown in pure culture from the lung. Boller reported the case of a 21 year old woman in whom one week post partum a pleural effusion developed which led to empyema. S. suipestifer was grown from the fluid. The patient was entirely well four months later. Van der Hoeden and Hulst obtained the organism from the pleural fluid and sputum of their patient.

The combination of pneumonia and articular involvement is an interesting one. Four cases of such a combination are on record.[4] Three were in infants 1, 5 and 15 months old, respectively. The articular infection developed from six days to six weeks after the pneumonia had become manifest.

4. Teveli; Tur and Gartoch, and van Creveld and Ruys.

Pyarthrosis and Osteomyelitis Due to S. suipestifer.[5]—In fifteen of seventy-one cases in which the diagnosis was proved by culture manifestations of involvement of the bones or joints were noted—an incidence of over 20 per cent. Only one of these cases was from the present series, but at the present time there is in this hospital a patient with S. suipestifer infection of the spine, a child who is not included in the present report. Seven of these patients were in the first year of life. The mortality in this group was 28 per cent. The sexes were equally affected; twelve were white, one was a Negro and one a Chinese.

The individual joints were involved as follows: knee—left in two, right in two; shoulder—left in two, right in four; ankle—left in two, right in one, and more than one joint in five cases. Two cases of osteomyelitis involving almost every bone in the body have been described (Matrossoff). One of these is included in the present series.

In the majority of these cases articular involvement was the first symptom of note. However, in several it appeared as a complication during the course of S. suipestifer septicemia from eight days to one month after the onset, usually being preceded by bronchopneumonia.

Case 7 of this series is of unusual interest because of the development of extensive purpura on the sixth day of illness and of osteomyelitis involving almost the entire skeleton before the fatal termination of the three month illness.

There is a period varying from a few days to several weeks before any objective evidence of articular involvement appears during which general malaise and difficulty in using the affected extremity are present. Only occasionally is a history of trauma to the joint elicited. Most of the patients have a remittent fever of varying degree, but several have been almost afebrile. On examination the involved joint is usually visibly swollen and warm. Occasionally the overlying skin is erythematous, tenderness to palpation is noted and movement is painful. Fluid is present in almost every case, and on aspiration a turbid, purulent, greenish material is obtained from which a pure culture of S. suipestifer is grown. Thus, the common finding is pyarthrosis. Osteomyelitis of the adjoining bone is not of infrequent occurrence.

Roentgenograms in the early stages may show nothing abnormal, but later such changes as periosteal thickening, rarefaction and erosion of the adjoining bone almost invariably appear. In case 7 of this series roentgenograms at first showed nothing abnormal, but, later, osteomyelitic changes were observed in almost every portion of the skeleton.

5. Bruin and Janssen; Dijkstra; Dijkstra and van der Hoeden; Gajzágó and Göttche; Kuttner and Zepp; Langwill; Nabarro, White, Dyke and Scott; Teveli; Tur and Gartoch; Weaver and Sherwood, and Weil and Saxl.

In contrast to the cases of uncomplicated bacteremia, well marked leukocytosis was noted in five of seven cases, the count ranging from 16,000 to 28,000. In four of the fourteen patients the organism was cultured from the blood stream.

In all the fatal cases there was extensive, multiple bony involvement. No case of monarticular involvement proved fatal. In one case death occurred seven weeks after the onset of articular lesions, and at autopsy no pathologic changes could be seen.

After open drainage or repeated aspiration of the joint, together with traction or immobilization, as indicated, the temperature drops rapidly to normal, the swelling gradually subsides and in from three to six weeks free mobility usually returns. Occasionally, slight limitation of motion remains, but in many of the patients followed for from six months to two years complete function was reestablished.

In a report by Ssokoloff there were mentioned thirty cases of surgical complications. Most of these were diagnosed by agglutination reactions with stock serums of the Glässer-Voldagasen strain, similar to that found by Neukirch (1918) in his cases. The manifestations were similar clinically, roentgenographically and pathologically to those of typhoid and paratyphoid osteomyelitis.

Five cases of spondylitis, all in men between the ages of 17 and 46, were noted by Ssokoloff. The process in two began directly after the febrile illness, but in one case a latent period of three months was noted. The first patient to be seen in this country with S. suipestifer infection of the spine is a patient who is in this hospital at the present time.

In ten cases infection of the costal cartilage was noted, all such instances occurring in men aged from 17 to 37, in whom the latent period varied from one week to two months. In three cases multiple foci were present. Serum agglutination titers varied from 1:200 to 1:1,600, and from an abscess which developed in one case a pure culture of the gram-negative rod was obtained. In two cases fistulas developed.

Articular involvement showing a predilection for the amphiarthrosis type was noted. With the exception of a 10 year old girl, the patients were men from 17 to 37 years of age. There was always a history of preceding febrile illness, followed in from one week to two months by articular manifestations. The sacro-iliac joint was involved in four cases, the sternoclavicular joint in two, the hip joint in three, the knee joint in two and the symphysis pubis in one. Pain on active and passive motion and swelling and pain on palpation of the capsule were usually noted, and free fluid was present in the joint. In three instances the organism was cultured from the synovial fluid. Healing occurred in from five to nine months.

Arssenjeff established the causal relationship of this organism in ten cases of articular infection. The involvement was mild, as evidenced by the average duration of illness of only two weeks. The bacillus was recovered in only one case; in this case there was an abscess around the ankle joint. The remainder of the cases were proved by serum agglutination tests.

Matrossoff reported a case of multiple osteomyelitis in a 25 year old man. The series of complications appeared at intervals of from three weeks to one year after the acute infection.

Infection Complicating Surgical Procedures.—Of special interest is the occurrence in this series of several cases of postoperative infection due to S. suipestifer. Kuttner and Zepp in 1933 reported a case of S. suipestifer bacteremia in which bronchopneumonia and cystitis occurred the day after a bilateral antral operation on a 28 year old Negress. Cultures of material from the sinuses and from the nose and throat were sterile, but the organism was obtained from the urine. The patient recovered. In one of Kuttner's cases, that of a 6 year old Negress with a three day history of abdominal pain, vomiting, fever, boardlike abdomen and a leukocyte count of 30,000, laparotomy was performed and the only finding was a small amount of fibrinous pus in the pelvis. After the operation the temperature remained high, and culture of the blood showed S. suipestifer. Hicks and Robertson described the illness of a Chinese police constable who, five days after drainage of an ischiorectal abscess, became ill, with fever, epigastric pain, a palpable spleen and mild leukocytosis. S. suipestifer was cultured from the blood stream. The illness terminated fatally.

In the present series there were several cases in which a relationship to some surgical procedure was noted. In case 16, that of a 33 year old Negress, bronchopneumonia of the upper lobe of the right lung developed after laparotomy for myomas of the uterus. The organism was cultured from the blood but not from the sputum. Later an indurated area in the wound was incised, and there was a moderate amount of serosanguineous pus, from which a pure culture of S. suipestifer was obtained. In case 19, that of a 36 year old Negro, acute pancreatitis was noted at operation. The temperature rose to 104 F. eight hours after operation, and death resulted within a few days. Unfortunately no cultures were made at the time of operation, but after death the organism was obtained from the heart blood and also from material from the peritoneal cavity. In several reported instances [6] S. suipestifer has been cultured from the bile of patients with cholecystitis and of patients supposedly ill with catarrhal jaundice. Whether or not infection of the biliary tract due to suipestifer was present in this case before

6. Ssokoloff and Waldman.

operation is impossible to say. Finally, in case 20, that of a 37 year old Negress with myomas of the uterus and B. coli cystitis, a high fever with chill developed on the second day after a cystoscopic examination. S. suipestifer was repeatedly cultured from the blood but never from the urine. No source of infection could be found in any of these patients.

Involvement of the Nervous System.[7]—Four fatal cases of purulent meningitis due to S. suipestifer are on record. In one case the organism was cultured from the spinal fluid and in three cases from the meningeal pus at autopsy. Coma, convulsions, purposeless movements of the hands, cervical rigidity, hypertonicity and a positive Kernig sign were noted. All the patients were in coma on admission, and the progress to death was rapid.

Boller reported the case of a 36 year old woman with bacteremia who on the fourth day of the illness showed signs of paralysis which he stated were like those seen in diphtheria. These gradually disappeared, and complete function returned within a few weeks.

In the Offenbach epidemic, reported on by Schnitter, many of the patients had slight disturbances of the peripheral nerves. Cervical rigidity was noted in a few. Also, transient deafness and trigeminal neuralgia occurred.

Endocarditis.—Gouley and Israel observed the following unusual case: In a 4 year old white girl a febrile illness developed, with marked prostration, five days before her admission to the hospital. Forty-eight hours after her entry into the hospital consolidation developed in the upper lobe of the right lung and on the ninth day of illness a double aortic murmur was audible. The blood culture showed S. suipestifer. The temperature returned to normal on the twelfth day of hospitalization, and the aortic murmur later disappeared. It was assumed that the patient had endocarditis due to S. suipestifer.

As a Secondary Infecting Agent in Association with Tumor.—Van der Hoeden and Hulst reported the case of a 16 year old boy who was ill for six months with enlargement of the lymph glands in the neck, widening of the mediastinum and enlargement of the spleen. The organism was cultured from material obtained by puncture of the growth, from the blood and the pleural fluid, once from the stool and regularly in the urine. The serum agglutination reached a titer of 1:12,800. At autopsy the tumor was described as an endothelioma.

Case 21 of this group is somewhat similar. S. suipestifer bacilli were grown repeatedly from the blood of this 70 year old woman during her illness. An agglutination titer of 1:1,280 developed, and at autopsy

7. Kuttner and Zepp; Materna and Januschke, and Neukirch.

a secondarily infected hypernephroma was present, from which the bacillus was obtained. Cultures of the urine and stool during life were sterile.

Predominant Infection of the Urinary Tract.—Although mild cystitis is not uncommon during the course of suipestifer infection, an infection of the urinary tract as the predominant feature of the clinical picture is distinctly unusual. Pyelitis has been reported (Ssokoloff). Neukirch (1918) described a case of pyelonephritis in a 26 year old man due to the Glässer-Volgadsen type of S. suipestifer. Ssokoloff reported a case of perinephric abscess which came to necropsy after a stormy illness of one month. A pure culture of S. suipestifer was grown from the pus.

THE BLOOD PICTURE

The reports in the literature are so meager in regard to the blood that chief reliance must be placed on the cases reported from this hospital. Table 3 displays the average white cell count at the time of the

TABLE 3.—*Leukocyte Counts*

	Typhoid-Like Picture	Pulmonary Involvement	Joint Involvement
Number of cases	19	16	8
Average	6,800	14,080	16,800
Highest	14,600	80,000	28,040
Lowest	1,700	3,800	4,900
Number above 10,000	1	6	5
Number below 5,000	6	3	1

patient's admission to the hospital in the various types of infection in our cases. It can be seen from these figures that leukocytosis is to be expected in patients with localizing signs of infection, while a normal or low count is usual in the patients with typhoid-like infection.

In contrast to cases of typhoid the development of complications during the course of suipestifer bacteremia is usually associated with marked leukocytosis. However, the white cell count in uncomplicated bacteremia tends to remain at a low level throughout the illness. In the cases among adults in which some associated disease was present the white cell count varied according to the nature of the accompanying illness.

A differential blood count has been made in so few proved cases that the following figures are of no great importance. In sixteen cases the averages were as follows: 11,800 white blood cells, 51 per cent polymorphonuclears, 41 per cent lymphocytes, 4 per cent monocytes and others 4 per cent. In eight of the cases the lymphocyte count exceeded 50 per cent. In only three instances was an increase in the number of young myeloid cells evident, and eosinophilia was reported once. The proportion of the various types of cells bears no relation to the height

of the white cell count during the course of the illness, except in the presence of an initial lymphocytosis, which disappeared rapidly in most instances at the end of the febrile period.

A slight degree of anemia is a frequent finding. The average hemoglobin value at the time of admission in the present series was 75 per cent, with 4,200,000 red blood cells. In most of the cases the anemia progressed slowly during the acute stage of the illness, but after the termination of the attack the normal level was soon reached. This progression in the anemia was often observed, even when small repeated blood transfusions were being given.

BACTERIOLOGY

S. suipestifer is a gram-negative motile rod which gives the sugar fermentation reactions of the paratyphoid B group but can be differentiated from this organism by its failure to ferment arabinose, trehalose and inositol (Kuttner and Zepp). Andrewes and Neave showed by absorption tests that there are two groups of suipestifer organisms. Those of group 1 are diphasic, in that they contain two types of antigen, the specific antigen which characterizes it and the nonspecific antigen which it has in common with group 2. Group 1 is the so-called American type described by Theobald Smith, and the Western European strains are usually of the group 2 type. In the literature several strains are described by name which are culturally and serologically related closely enough to be included in the present report: (1) the American type, (2) the Kunzendorf, or Western European, type, (3) the Glässer-Voldagsen type and (4) the Oriental, or Eastern, type. All of these strains are pathogenic for animals, in which respect they differ from the closely related paratyphoid C bacillus described by Hirschfeld.

Cross-agglutination with other members of the group is so frequent that when ordinary laboratory diagnostic serums are used one may be led to a false conclusion as to the causal organism. It seems reasonable to assume that in instances in which one is not aware of the possibility of suipestifer infection an illness due to this organism might incorrectly be diagnosed as parathyphoid fever. In case 21 of the present series paratyphoid B agglutinations were complete with the stock serums as high as 1 : 1,280, and only after additional sugar reactions were studied and more detailed serologic reactions were undertaken was the correct identity of the organism established.

A thorough knowledge of the serologic classification of the paratyphoid group of organisms is necessary for the exact identification of the bacterium. By absorption a type-specific serum can be produced which can serve to identify any strain by direct agglutination if a reasonable number of organisms in the type phase are present. On the

other hand, identification of a group culture will depend on the proper absorption of various type serums to remove type agglutinins for the homologous strains (Topley and Wilson).

Recognition of the possibility of cross-agglutinations together with further sugar tests will serve in most instances for the proper recognition of S. suipestifer.

Blood Culture.—Blood culture is the usual method by which the diagnosis is made evident. It is fortunate that these organisms can be grown from the blood with relative ease and that bacteremia persists for a relatively long period. In fifty-three, or 74 per cent, of the seventy-

TABLE 4.—*Organisms of Salmonella Group (After Topley and Wilson)*

Species or Type	O Antigens (Somatic)	H Antigens (Flagellar)		
		Type	Group	
Paratyphosus B	I II	Paratyphosus B	G	A
Stanley	I II	Stanley S	G	A
Aertrycke	I II	Aertrycke	G	A B C
Newport	IV	Newport D_1 D_2	G	A B C
Reading	II	Reading D_1 D_2	G	B—
Morbificans bovis	IV	Morbificans bovis	G	E_1 E_2
Suipestifer (diphasic)	V	Suipestifer W W_1	G	B E_1 E_2
Suipestifer (monophasic)	V	Suipestifer None	G	B E_1 E_2
Hirschfeld	V	Hirschfeld W W_2	G	B— E_1 E_2
Sendai	XI	Sendai T	G	E_1
L	IX	L M_1 M_2	G	

TABLE 5.—*Data on the Blood Cultures*

Day of Illness	Reported Cases		Present Series				
	No. of Cases	No. of Positive Cultures	No. of Cases	No. of Cultures Made	No. of Positive Cultures	No. of Sterile Cultures	Positive Cultures, %
1- 7	28	32	7	10	8	2	80
8-14	11	12	10	13	11	2	
15-21	5	6	6	7	5	2	
22-28	1	2	3	3	1	2	33

one proved cases, including the twenty-one cases in the present series, blood culture showed positive results at some time during the course of the disease. From those cases in which the day of onset of the disease could be fairly accurately determined the figures presented in table 5 were secured.

In contrast to most infections the bacteremia which is so commonly seen in this disease persists for long periods, yet metastatic lesions are relatively infrequent. Thirty-three per cent of the cultures taken during the fourth week of the disease showed positive results.

The highest number of organisms per cubic centimeter of blood in any culture was 255. In this case the patient died. Sixty-five colonies per cubic centimeter were found in case 13 of the present series, which did not end fatally.

The Agglutination Reactions.—While the presence of S. suipestifer infection is usually proved by culture, agglutination of the serum of patients with unexplained fever has established the diagnosis in many cases. In thirty-four of the seventy-one proved cases, of which twenty-one were in the present series, a positive agglutination reaction developed. In many of the cases reported in the literature no agglutination tests were made, or they were attempted only once during the first week of the disease, so the foregoing figure is not accurate. Titers as high as 1:12,800 are found, and in case 16 of this series agglutination was strongly positive in a 1:10,240 dilution. Van der Hoeden and Hulst reported one case of pleural effusion in which the fluid obtained showed an agglutination titer of 1:400.

A rough idea of the agglutination titer during successive weeks of the disease can be obtained from table 6, which was compiled from the

TABLE 6.—*Agglutination Reactions*

Week of Illness	No. of Cases	Titer						Highest Titer
		0	80	160	320	640	1,280	
1	6	1	2	1	2	..	..	.....
2	10	5	1	1	2	1	..	.....
3	14	1	2	2	5	1	2	1:4,000
4	9	2	..	..	4	2	2	1:4,000
5	2	..	..	..	..	1	..	1:4,000
6	4	..	1	..	..	1	1	1:5,000
7	1	..	..	..	..	..	..	1:5,000

cases of the present series and a few obtained from the literature. In the present series of cases 88 per cent of the patients showed an agglutination titer higher than 1:320 by the fourth week. In seventeen of eighteen cases positive results were obtained, and in only one was the titer less than 1:160. In the dilutions mentioned practically complete agglutination occurred.

Few figures are available concerning the duration of demonstrable agglutinins in the blood. In one case a titer of 1:250 was still present two years after the acute illness occurred. Titers of 1:500 eight months after recovery are known, and agglutination in a dilution of 1:2,000 may persist for as long as two months.

PATHOLOGY OF S. SUIPESTIFER INFECTIONS

There are no specific lesions which are attributable to infection by this organism. Acute splenic tumor, petechial hemorrhages in the serous membranes and cloudy swelling of the liver and kidneys are often present. Focal areas of necrosis in the liver similar to those seen in cases of typhoid are frequently present.

In the majority of cases no intestinal lesions can be discovered, and the organism cannot be grown from the intestinal contents. Involvement of the lower portion of the ileum and large intestine, with ulceration of the mucous membrane and enlargement of the mesenteric lymph nodes, has been described, but complete bacteriologic studies of the intestinal contents were not carried out in these cases, and they may have represented coexisting infection by some other organism (Neukirch, 1918).

Although the organism can often be obtained in pure culture from material from the lungs, bones and joints, kidneys, meninges and other lesions, the observations at autopsy are neither grossly nor microscopically specific for infection with S. suipestifer. The organism can usually be cultured from the heart blood, the spleen and elsewhere as a secondary invader in a preexisting disease state.

COMMENT

It seems reasonable to assume that infections in human beings due to S. suipestifer are far more common than is generally recognized. In numerous cases a diagnosis of paratyphoid fever is undoubtedly made. If in every bacteriologic laboratory the correct identification of organisms belonging to the paratyphoid B-Salmonella group were faithfully pursued the evidence of suipestifer infection would probably increase to a considerable degree.

Associated with Other Diseases.—As most of the strains of S. suipestifer are not of great virulence, the frequent occurrence of other diseases in this group of infections is not surprising.

During the war outbreaks of this infection went hand in hand with poor nutrition, as manifested by scurvy, and severe exposure to cold and wet. The associated infection with plasmodia and the spirochete of Obermeyer is not uncommon. The organism finds fertile soil in a person whose resistance is lowered by the presence of another disease or in a young infant, whose powers of resistance are not great. Köbe reported the appearance of a subcutaneous abscess due to this bacillus in a 59 year old diabetic patient. Bosch commented on the increased incidence of the infection on the east coast of Sumatra during an epidemic of pneumonia among young children. He noted, too, the frequent occurrence of combined malarial and Salmonella infection. Numerous other diseases might be mentioned which have been associated with suipestifer infection: gonococcic urethritis, arthritis, ischiorectal abscess, periuretheral abscess due to B. coli, endothelioma and bacillary dysentery.

Other diseases found in the present series are as follows: rickets, mediastinal tuberculosis, pharyngitis due to beta hemolytic streptococci, congenital heart disease, rheumatic heart disease with myocardial failure

(a pure culture of S. suipestifer was obtained in one case from the pericardial fluid), pregnancy, B. coli cystitis, myomas of the uterus and hypernephroma.

Transmission from Contact and Among Members of the Same Family.—Tur and Gartoch described the illness of a 1 month old child which was characterized by pneumonia and articular infection. S. suipestifer was cultured from the stool and synovial fluid. Eighteen days after delivery the mother had a "typhoid-like infection," but no bacteriologic study was made. Suspicion of a relation of the infection in this case to the mother by transmission by means of the blood or milk was entertained but not established.

The patient reported on by Haynes and Meiks became sick during a period when the hogs on the farm were ill with cholera.

In one of Kuttner's cases the parents gave a story of a febrile illness resembling that of the patient, and the mother's serum agglutinated the organism obtained from the blood of the patient. In a second case the mother's serum agglutinated the patient's organism 1 : 80.

In case 6 of this series the patient had the infection in March 1935, and her cousin (case 10) had it the following May. The brother of the sixth patient was ill in the middle of May with fever, abdominal pain and headache. However, agglutination of the serum from eight members of the family proved negative. Culture of the stool from both patients was consistently sterile, and no known source was discovered.

The difference between the infection as seen in adults and that in children is striking. The incidence is higher, the course is milder and the number with articular manifestations is greater among those of the younger age group. In contrast to childhood infection, association with some usually more important disease is found with great regularity among adults.

SUMMARY

The literature on S. suipestifer infections in human beings is reviewed, and twenty-one new cases are reported.

Epidemic outbreaks of food poisoning due to a known source of infection are common, but the infection is usually mild, and the mortality is low.

Sporadic cases occur with some frequency in Baltimore.

Uncomplicated bacteremia simulating typhoid is the most common type of infection.

In some cases the predominant feature of the clinical picture may be pneumonia, osteomyelitis, pyarthrosis, meningitis, endocarditis or severe infection of the urinary tract.

Several cases of infection complicating surgical procedures are described.

It is believed that in cases of infection due to this organism a diagnosis of paratyphoid fever is sometimes made, because of the frequency with which cross-agglutinations in high dilutions with paratyphoid B antiserum occur.

The organism can be grown readily from the blood stream, and the bacteremia often persists for a long time. In the present series 88 per cent of the patients had an agglutination titer of 1 : 320 by the fourth week of illness.

Thus far no specific pathologic lesions attributable to infection by this organism have been described.

In children the incidence is higher, the course is milder and the number of articular manifestations is greater.

In adults there is frequently an associated disease which is of primary importance.

In the majority of the sporadic cases there is no recognizable source of the organism in the body, and the manner of entrance is usually entirely unknown.

The majority of cases of suipestifer bacteremia occur during the first decade of life. For patients less than 25 years of age the mortality was 19 per cent, while for those over 25 it rose to 58 per cent.

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TREATMENT OF ESSENTIAL HYPERTENSION WITH A DEPRESSOR SUBSTANCE PREPARED FROM THE URINE

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The treatment of essential hypertension with depressor drugs has been disappointing. The use of depressor substances that are present normally in the body, such as choline, acetylcholine, histamine, adenosine and its derivatives and guanido-acetic acid, has not been extensively investigated, owing primarily to the fact that unpleasant or toxic symptoms accompany their administration. However, there are theoretical reasons for believing that one of these substances, to which the name kallikrein has been given by its discoverers, may be of value in lowering a pathologically high blood pressure. The physiologic and chemical properties of this substance have been discussed in previous publications.[1] This principle is presumably elaborated by the pancreas; it circulates in the blood stream and is eliminated in the urine, where it is present as a thermolabile colloid with certain rather distinctive biologic reactions on which its identification rests. These reactions are a fall in the blood pressure, with an increase in the amplitude of cardiac contraction, after intravenous injection into an experimental animal, and an antagonism to the pressor effect of epinephrine when injected simultaneously with it. The theoretical basis for its further trial lies in the fact that

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1. Kraut, H.; Frey, E. K., and Werle, E.: Ueber die Inaktivierung des Kallikreins, Ztschr. f. physiol. Chem. **192**:1, 1930. Frey, E. K.; Kraut, H., and Werle, E.: Ueber die Blutzuckersenkende Wirkung des Kallikreins (Padutin), Klin. Wchnschr. **11**:846 (May 14) 1932. Frey, E. K.: Kallikrein (Padutin) im Blut, München. med. Wchnschr. **80**:125 (Jan. 27) 1933. Kraut, H.; Frey, E. K.; Werle, E., and Schultz, F.: Nachweis und Vorkommen des Kallikreins im Harn, Ztschr. f. physiol. Chem. **230**:259, 1934. Elliot, A. H., and Nuzum, F. R.: The Pharmacologic Properties of an Insulin-Free Extract of Pancreas and the Circulatory Hormone of Frey, J. Pharmacol. & Exper. Therap. **43**:463, 1931. Nuzum, F. R., and Elliot, A. H.: Insulin-Free Pancreatic Extract and the Circulatory Hormone (Kallikrein of Frey and Kraut), California & West. Med. **39**:361 (Dec.) 1933.

its average concentration in the urine of a group of persons with essential hypertension was found, particularly in young subjects, to be considerably below normal.[2] This suggested that if the concentration in the blood of this depressor principle were raised in such subjects by hypodermic injection, a decrease in the blood pressure might result, particularly if by this means a true substitution therapy had been evolved.

The continental literature[3] contains a number of favorable reports regarding the use of the depressor substance called kallikrein in the treatment of hypertension. Frey,[3a] who has most forcibly called this drug to the attention of the members of the medical profession, mentioned four patients with fixed hypertension in whom the blood pressure fell for a period of from six to eleven months after a series of injections. The most enthusiastic paper was that of Scharpff,[3b] based on the study of thirty institutional patients in whom the usual methods of therapy had been used without avail. After from eight to ten injections a fall in the blood pressure occurred in all the patients, except those with malignant hypertension or contracted kidneys. The author stated that he believed that this substance acts physiologically in the manner of a hormone and is the best means yet available for lowering the pathologically high blood pressure.

A substance called vagotonine,[4] a preparation made from the pancreas and probably different from the substance called kallikrein, has recently been reported as a most satisfactory drug for the treatment of hypertension.

This paper is a summary of the response of the blood pressure of a group of hypertensive patients to intensive and prolonged medication with a depressor substance prepared from the urine.[5]

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2. Elliot, A. H., and Nuzum, F. R.: The Urinary Excretion of a Depressor Substance (Kallikrein of Frey and Kraut) in Arterial Hypertension, Endocrinology **18**:462 (Aug.) 1934.

3. (*a*) Frey, E. K.: Kreislaufhormon und innere Sekretion, München. med. Wchnschr. **76**:1951 (Nov. 22) 1929. (*b*) Scharpff, W.: Die Behandlung der Hypertonie mit dem Frey-Krautschen Kreislaufhormon Padutin (Kallikrein), Deutsche med. Wchnschr. **57**:675 (April 17) 1931. (*c*) Leschke, E.: Erfahrungen mit dem Kreislaufhormon Kallikrein, München. med. Wchnschr. **77**:1524 (Sept. 5) 1930. (*d*) Binswanger, H.: Einige Beobachtungen mit dem neuen Kreislaufmittel "Kallikrein," Deutsche med. Wchnschr. **57**:1057 (June 19) 1931. (*e*) A New Internal Secretion of the Pancreas, foreign letter, J. A. M. A. **95**: 676 (Aug. 30) 1930.

4. Marklen, L.; Vidacovitch, M., and Franck, C.: Physiologic Basis of Therapy by Vagotonine (Pancreatic Hormone), Presse méd. **41**:1745 (Nov. 11) 1933.

5. The preparation used was essentially the same as that which Frey described and called kallikrein.

METHODS AND SUBJECTS

Methods of preparing this principle from urine have been reported in detail elsewhere.[6] The first batches were made after the method of Frey; these were crude and when given resulted in local subcutaneous reactions. Later batches became pure, and a concentration of units up to 10,000 per milligram of dried material was obtained. This substance when dissolved could be given in large doses subcutaneously without producing a local or a systemic reaction. The material was given daily or thrice weekly by intramuscular injection in doses varying from 50 to 5,000 biologic units over a period of weeks or months, to reach a total dose of from 2,300 to 64,000 units. No immediate response of the blood pressure or toxic reaction was observed. Occasionally after from six to twenty-four hours mild systemic protein reactions occurred, which, with the purer preparations now at our disposal, have been obviated.

The subjects treated were carefully chosen. Seven of them, four of whom were males, were less than 40 years of age. Four of these patients were suffering from an early stage of essential hypertension. The blood pressure in each case was occasionally within normal limits, but the frequent occurrence of fairly high systolic readings, together with a slight degree of cardiac enlargement, justified the diagnosis of hypertension. This group of patients was watched over for a long time with particular interest because the urinary output of the depressor substance was below normal and because, with the possible exception of one patient, who was suffering from mild thrombo-angiitis obliterans, the disease was unaccompanied with vascular degeneration. Each of the remaining six patients, three of whom were more than 40 years of age, had a higher and more fixed blood pressure and showed some evidence of organic vascular changes.

The true evaluation of any therapeutic measure in essential hypertension is a difficult matter, and results are easily misinterpreted unless a suitable technic of investigation is scrupulously adhered to. The present study was therefore conducted in the following manner: 1. Readings of the blood pressure were made by the same observer at the same time of day for each patient. Before a reading was made the patient rested for ten minutes in a semidarkened room. 2. Control determinations were made over a period of at least ten days before the injections were started. 3. No medication other than the depressor substance was given, except for injections of colored water as a part of the control observations. 4. The total period of observation was at least fifty days, while several of the patients were followed for over a year. 5. Psychic suggestion was carefully avoided in every instance, each patient understanding that he was subjecting himself to an experimental investigation which might well prove of no benefit. For these reasons the group was necessarily small. 6. The data were discarded for any patient in whom some disturbing environmental influence, such as intercurrent illness or family worry, appeared. Enough blood pressure readings were taken during the control, treatment and follow-up periods to allow a satisfactory statistical analysis in each case.

RESULTS

In the accompanying table the mean blood pressure and the length of the control, treatment and follow-up periods, together with other pertinent data, are given for each patient. The standard deviations, as a measure of the predictable variability of the average blood pressure

6. Bischoff, F., and Elliot, A. H.: Purification of the Depressor Colloid of Urine (Kallikrein), J. Biol. Chem. **109**:419 (April) 1935.

Data on the Response of the Blood Pressure to Injections of a Depressor Substance

			Control Period			Treatment Period				Follow-Up			
Name	Age	Sex	Duration	No. of Determinations	Mean Blood Pressure	Duration	No. of Determinations	Total Dose, Units	Mean Blood Pressure	Duration	No. of Determinations	Mean Blood Pressure	Comments
A. W.	26	F								.....	..	.....	Total period of observation, 29 mo.; early essential hypertension; blood pressure frequently 150 or 160 mm. of mercury; two normal pregnancies during this time; previously had had two pregnancies, with hypertension and abortion
Period 1			11 days	8	143 ± 1.5 / 84 ± 1.7	35 days	27	8,255	127 ± 1.3 / 76 ± 0.4				
Period 2			11 days	10	127 ± 1.6 / 76.5 ± 1.6	24 days	11	4,225	125 ± 0.1 / 76.1 ± 1.3				
Period 3			5 mo.	60	127 ± 1 / 79 ± 1	11 days	9	2,336	142 ± 4.5 / 92.5 ± 2				
Period 4			8 mo.	21	136 ± 1.1 / 80 ± 1.3	22 days	14	4,400	127 ± 2.4 / 83 ± 3.1	12 mo.	22	138 ± 1.3 / 78.6 ± 1	
F. S.	29	M	12 days	6	144 ± 2 / 84 ± 1.8	53 days	33	45,250	144 ± 1.5 / 78 ± 1	24 mo.	4	145-155 / 80-95	Early essential hypertension; mild Buerger's disease
E. W.	34	M	46 days	21	175 ± 4 / 124 ± 2	48 days	32	64,000	173 ± 2.5 / 129 ± 1	24 mo.	5	180-200 / 125-135	Cerebral hemorrhage at end of treatment period
W. R.	40	M	21 days	12	138 ± 3.7 / 98 ± 1.2	37 days	24	25,375	126 ± 1.3 / 86 ± 1.5	3 mo.	38	126 ± 2.4 / 87 ± 1.4	Early essential hypertension
J. K.	27	M	30 days	18	152 ± 0.9 / 103 ± 1	20 days	11	3,700	151 ± 1.6 / 100 ± 1.4	.....	..	.....	
E. A.	23	F	10 days	10	147 ± 2 / 82 ± 1.5	5 mo.	46	43,750	147 ± 1.2 / 86 ± 0.9	3 mo.	4	150-155 / 0-40	Hyperthyroidism developed during follow-up period; also had small coronary occlusion
M. T.	24	F	12 days	12	147 ± 2.5 / 88 ± 1	4 mo.	35	27,100	147 ± 0.8 / 86 ± 1	.....	..	.....	Early essential hypertension
R. T.	60	F	12 mo.	13	183 ± 1.3 / 97 ± 2.5	9 mo.	19	2,400	184 ± 3.0 / 92 ± 1.3	.....	..	186 ± 3.8 / 99.5 ± 2.5	Total period of observation, 6 yr.; onset and developement of hypertension watched; finally diabetes developed (1934)
M. W.	53	M	6 mo.	10	195 ± 3 / 130 ± 2.3	3 mo.	7	2,350	220 ± 2.6 / 120 ± 3	18 mo.	15	211 ± 2 / 135 ± 1.5	
G. G.	43	M	1 mo.	6	205 ± 11.7 / 133 ± 4	8 mo.	75	10,000	190 ± 1.5 / 125 ± 1.1	.....	..	.....	

during these periods, have been calculated. In general the results are disappointing. Only two patients (A. W. and W. R.) showed a significant fall in the mean blood pressure during or following the period of treatment. That the magnitude of the fall in these subjects was slight, even though fairly consistent, is well illustrated by chart 1 (W. R.). Since the blood pressure of each of the remaining patients did not change, we are inclined to attribute this result to some alteration of factors in the environment of these patients which was beyond our knowledge and control.

No appreciable amelioration of symptoms was evident in our patients as the result of the administration of the depressor substance. During the period of treatment one patient had a cerebral hemorrhage, and

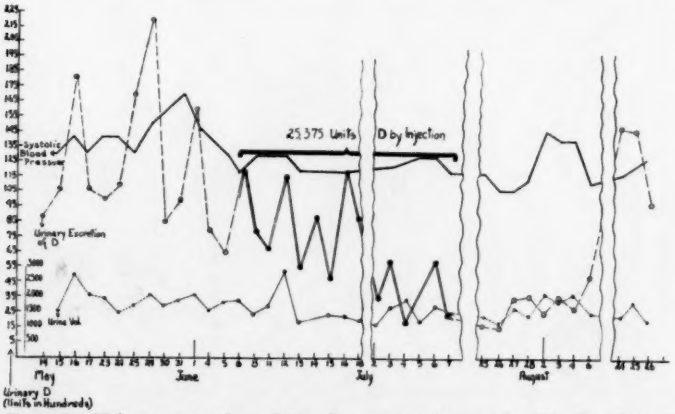

Chart 1.—Urinary excretion of the depressor substance by W. R. Note that the fluctuations are independent of the volume of urine excreted. In charts 1 to 3 *D* represents the depressor substance.

another had coronary occlusion. It is unlikely that there was any causal relationship, but these accidents indicated that the natural course of the malady was not stayed by this method of treatment.

Changes in the Urinary Output of the Depressor Substance.—The concentration of the depressor substance in the twenty-four hour specimens of urine was determined daily before, during and after treatment in four instances (F. S., E. W., W. R. and J. K.). The changes in the output of urine were of two general types, as shown in charts 1 and 2. In the case of W. R. (chart 1) the daily concentration of the depressor substance fluctuated widely during the control period, but the average output was less than that of a normal subject of the same age. Shortly after treatment was begun the concentration began to fall, until at the conclusion of the treatment period it had decreased by approximately

80 per cent, at which level it remained for one month. It will be noted that this change was not dependent on a lessened volume of urine. Studies of the renal function, initially showing an excellent renal reserve, were not conducted during the time that the urinary output of the depressor substance was low, so it is impossible to say whether a temporary impairment of renal function existed. It is of interest that the blood pressure was slightly lowered during the period of treatment in this instance. In chart 2 a more irregular type of response is illustrated. The urinary concentration of the depressor substance rose during the early days of treatment from an extremely low initial level. The curve for the excretion then became roughly diphasic. After sinking

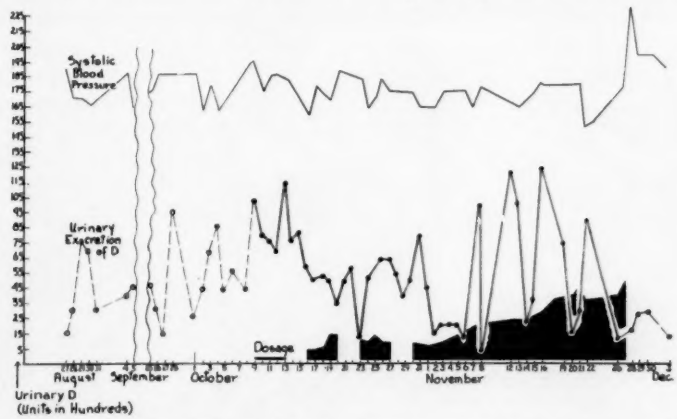

Chart 2.—Urinary excretion of the depressor substance by E. W. The period of treatment is represented by double lines and solid circles.

to the control level it rose above this toward the end of the period of treatment, when large doses of the depressor substance were being given. There was no significant change in the blood pressure, except for a final rise when apoplexy supervened. The rate of excretion in the remaining two instances was inconstant, but the shape of the curve was in general similar to that shown in chart 1.

In an attempt to study this matter further, the depressor substance was given to rabbits by the intramuscular and intravenous routes. The total excretion of urine, as measured from samples collected over periods of three days, was followed. A typical protocol is illustrated by chart 3. While the injections were being given there was a pronounced increase in the urinary content of the depressor substance, which in one specimen was twice that of any specimen collected during the control period. The total increase was several times greater than could be accounted for by the total amount of the depressor substance injected. When the

drug was given by the intravenous route, the urinary concentration was extremely depressed during the period of injection and rose to, but not above, the control level when the injections were stopped. We cannot satisfactorily interpret these results, and it is likely that an adequate explanation will not be forthcoming until the level of the depressor substance in the blood can be successfully determined.

It should be added that the samples of urine were tested for depressor activity both before and after boiling. In conformity with our previously reported results, we found that approximately one fourth of the depressor principle was heat stable and that this relationship for the most part held true regardless of fluctuations in the total amount of depressor substance excreted.

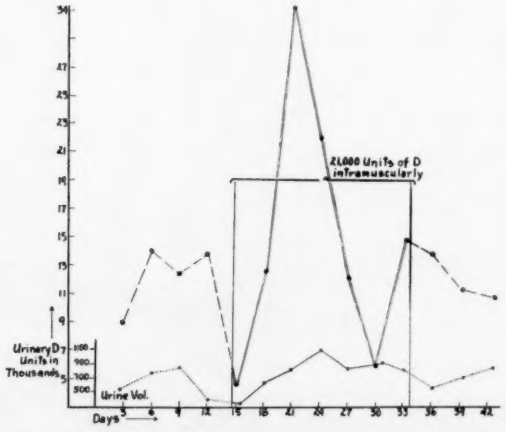

Chart 3.—The effect of the intramuscular injection of the depressor substance into a rabbit on the amount excreted in the urine. The period of injection is represented by double lines and solid circles.

COMMENT

The inability of this method of treatment consistently to lower the blood pressure of the patients needs no further comment. The observations on the urinary excretion of the depressor substance have proved disappointing, in that no uniform or predictable trend was discernible. At the outset of this study it was hoped that, coincident with a fall in blood pressure due to the administration of the depressor substance, its urinary output might rise to a normal level and thus confirm a causal relationship between the clinical result and the method of treatment employed. This would have suggested that a restoration to normal equilibrium between pressor and depressor elements of the blood stream

had been accomplished by a true substitution therapy. However, this attractive hypothesis was not confirmed by the results obtained in this study.

SUMMARY

A depressor principle prepared from the urine has been given hypodermically under carefully controlled conditions to ten patients with essential hypertension.

A slight but statistically significant fall in blood pressure resulted in two instances. The blood pressure of the remaining patients was not influenced.

The symptoms presented by these patients were not ameliorated, and there was no indication that the course of the disease was favorably influenced.

In four instances the daily urinary excretion of this substance was determined throughout the period of observation. No consistent change in the concentration could be demonstrated. Similar observations conducted on rabbits likewise were inconclusive.

The use of this principle hypodermically for the treatment of essential hypertension cannot be regarded as a substitutive therapeutic measure.

Progress in Internal Medicine

ALLERGY

A REVIEW OF THE LITERATURE OF 1936

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Another year has gone by since my last review [1] appeared; again a large number of papers on allergy have been published. The *Journal of Allergy* contains many of these. It has an abstract department which has been greatly improved and developed in a wider scope, and it includes also a series of special reviews on certain phases of the study of allergy. Hansel [2] has written on allergy as related to otolaryngology and ophthalmology; Feinberg [3] has reviewed the progress in asthma; Sulzberger [4] has written on allergy in dermatology, and Walzer [5] has reviewed the immunology of cutaneous tests. Each of these reviews is good.

In the following summary the selection and arrangement of the material must depend largely on my own personal interest, and I realize that this present combination can satisfy only the general reader. All who are really interested must go to the original sources, which are so easily available. If the attention of the reader, whether general or special, is guided into profitable channels, I shall be repaid for performing a difficult task.

Some progress has been made in the diagnosis and treatment of what may be called clinical allergy, but greater progress has been made in another direction. Allergic conditions, especially hay fever and asthma, are coming to be regarded not so much as separate diseases

From the Allergy Clinic and Laboratory, the Massachusetts General Hospital.

1. Rackemann, Francis M.: Allergy: A Review of the Literature of 1935, Arch. Int. Med. **57**:184 (Jan.) 1936.

2. Hansel, French K.: Annual Review of Allergy as Related to Otolaryngology and Ophthalmology: Literature for 1935, J. Allergy **7**:164, 1936.

3. Feinberg, Samuel M.: **Progress in Asthma**: Literature for 1934 and 1935, J. Allergy **7**:268, 1935.

4. Sulzberger, Marion B.: **Allergy in Dermatology**: A Discussion of Recent Contributions and Their Relationship to Earlier Dermato-Immunologic Studies, J. Allergy **7**:385, 1936.

5. Walzer, Matthew: Immunology: A Critical Review of Some Recent Developments in the Field of Allergy, J. Allergy **7**:597, 1936.

as the outward expression of a peculiar reaction which may after all be merely the exaggeration of a normal response. More and more evidence is at hand of the correlation of the reaction which is termed clinical allergy with similar reactions observed in infectious diseases as well as with other reactions observed in laboratory animals prepared and tested in particular ways. The base on which allergy rests is becoming broader, and the conception of the extent to which allergic reactions occur in the clinic is likewise broader. The relationship of hay fever, asthma, eczema and serum disease to acute infectious processes like pneumonia and trichinosis and to chronic infections like tuberculosis as well as to experimental anaphylaxis is being considered actively. It becomes evident that the study of allergy is not a narrow, specialized field but requires a broad understanding of the behavior of the animal body in its effort to rid itself of foreign proteins under many different conditions.

The immunity of the tissues as opposed to the immunity of the organism as a whole is receiving increased attention. The nature and particularly the function of the local response of the tissues to foreign materials of various kinds applied in various ways are being studied. In the review of last year considerable attention was paid to the observations of Jones and Mote [6] and others that when a guinea-pig is given repeated daily injections of a foreign protein, like egg white or horse serum, a local reaction is observed as early as the third or fourth day and consists of a red inflammatory lesion, corresponding to the tuberculin reaction. Later, on the seventh or eighth day, the local reaction changes to swelling and edema characteristic of the urticarial reaction which is associated with clinical allergy, and at this same time, too, antibodies first appear in the circulating blood. As Dienes [7] writes in an excellent review of this whole subject, "The first manifestation of the specific response . . . is not the appearance of the antibodies in the circulation but a hypersensitiveness of the tissues." The tissue response comes early and is independent of antibodies. It is not an inflammation in the strict sense but rather an attempt of the body to wall off and localize the infection. It is part of the resistance of the animal. It comes early in the process of immunization and before the development of circulating antibodies. This early tuberculin-like reaction is a function of the tissues themselves and is not in any sense a secondary response dependent on the arrival of antibodies in these tissues. In

6. Jones, T. Duckett, and Mote, John R.: The Phases of Foreign Protein Sensitization in Human Beings, New England J. Med. **210**:120, 1934.

7. Dienes, L.: The Specific Immunity Response and the Healing of Infectious Diseases: Significance of Active Immunity and the Connections Between the Immunity Response and the Anatomic Lesions, Arch. Path. **21**:357 (March) 1936.

this way, Dienes explains that the reaction called bacterial allergy represents a true phase in the development of the immune process. It is an indicator of active immunization of the tissues, and it gives rise to those anatomic lesions which serve to localize the infection. Dienes lays some stress on this and justifies his position in several ways, notably by saying that all attempts to produce the tuberculin-like reaction passively with immune serum have failed. This injection of such immune serum results only in the anaphylactic type of response. Desensitization may abolish the urticarial reaction temporarily, but in spite of this a resistance of the tissues persists and can be demonstrated at all times by appropriate treatment. The desensitized animal is not in the condition of a noninfected animal.

Reuben L. Kahn [8] has recently written a book of seven hundred pages on this subject. In it he too lays stress on the independence of tissue reactions, on the one hand, and systemic reactions as shown by the development of circulating antibodies, on the other. Like the latter, the former also may be highly specific. Kahn emphasizes that allergic reactions, indeed inflammation in general, have a function. The redness and swelling which develop at the site of inoculation represent primarily the effort of the tissue to fix the foreign substance or the bacterium and thus to prevent it from spreading throughout the host. This local immunity varies with certain tissues. The skin, for example, has a much greater reaction capacity (immunity) than does muscle. If staphylococci obtain a foothold in the skin, they are walled off quickly, and the danger to the body as a whole is slight; in the muscle, however, the local response is less violent, and walling off is less effcient. Hence, deep staphylococcic infections may be dangerous. The rôle of the tissues in the resistance of the animal is vital. From his studies of tissue reactions Kahn believes that hypersensitiveness, or allergy, is merely an exaggeration of the normal immune process.

The Shwartzman phenomenon is closely related to allergy, even though there is still doubt as to its true nature. When an animal (rabbit) is treated with toxin intracutaneously and then after an incubation period receives a dose of that same toxin intravenously, the treated cutaneous sites will show an extensive reaction, with severe inflammation and necrosis. As is well known, this reaction is produced by specific and also by nonspecific means. Jules Freund,[9] for example, has shown in rabbits that the intravenous injection of starch will cause a reaction to appear at the site of a previous intracutaneous dose of

8. Kahn, Reuben L.: Tissue Immunity, Springfield, Ill., Charles C. Thomas, Publisher, 1936.

9. Freund, J., and Hosmer, E. P.: Hemorrhagic Reaction [Shwartzman Phenomenon] at the Site of Injection of Toxins After Intravenous Injection of Starch in Young and Adult Rabbits, J. Immunol. **29**:279, 1935.

toxin. In another experiment he has shown that when filtrates of various organisms are injected intravenously the treatment will result in violent lesions at the site of previous cutaneous tests with tuberculin, horse serum or silver nitrate. Incidentally, these toxins cause much more reaction in tuberculous than in normal animals. By means of the Shwartzman reaction, various attempts have been made to explain the mechanism and clinical pictures of common diseases. Last year, for example, the interpretation of a syphilitic chancre on this basis was described. Now comes a report from Sanarelli [10] in a letter published in *The Journal of the American Medical Association,* that various acute disturbances characterized by hemorrhage and necrosis, such as cholera or even appendicitis, may depend on a local sensitiveness of the tissue, which is lighted up by the sudden presence of toxic substances in the blood stream.

In all studies of allergy in animals as well as in man, the experimental technic is of greatest importance. McEwen and Swift [11] describe their studies of the reactions of rabbits to the injection of bacterial substances. When their animals were treated intravenously, serum antibodies reached a high titer, but the extent of the cutaneous hypersensitiveness was only moderate. The cutaneous reactions were immediate and of an urticarial type. When, however, other animals were treated intracutaneously, hardly any circulating antibodies developed, while the cutaneous tests showed a strongly positive reaction of the delayed tuberculin-like type. When whole organisms, that is, formed elements, were used for the preparation, more circulating antibodies (precipitins) developed, and the cutaneous tests of the immediate type showed positive reactions to the protein P and the carbohydrate S fraction as well as to the whole organism. When, however, the original treatment was with the P fraction or the S fraction alone, then the reactions in both serum and tissues were chiefly to the particular fraction used. The work indicates that the induction of reactions of the immediate type requires something more than the presence of a high serum precipitin titer to the substance in question. Cutaneous reactions and serum antibodies are not always parallel.

Stevens and Jordani [12] describe the results of tests with various bacterial nucleoproteins in patients with asthma. They, too, show that

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10. Hemorrhagic Allergy, foreign letter, J. A. M. A. **107**:1825 (Nov. 28) 1936.

11. McEwen, C., and Swift, H. F.: Cutaneous Reactivity of Immune and Hypersensitive Rabbits to Intradermal Injections of Homologous Indifferent Streptococcus and Its Fractions, J. Exper. Med. **62**:573, 1935.

12. Stevens, F. A., and Jordani, L.: Behavior of Immediate and Delayed Cutaneous Reactions to Bacterial Nucleoproteins in Asthmatic Patients, J. Immunol. **31**:51, 1936.

delayed inflammatory reactions and immediate urticarial reactions are closely related, as will be described presently.

In making an analysis of experiments of this kind, the student must note several important points: the choice of animal, the treatment by which sensitiveness is produced and, finally, the material used and the method of application to elicit the reaction. Apparently it is true that the urticarial reaction occurs only when the preliminary treatment has resulted in the production of circulating antibodies. In animals inoculated with living organisms or with whole killed organisms (formed elements) immunity of this sort is produced and cutaneous tests of the immediate type can be readily demonstrated. When, however, the animals are treated with extracted material, such as bacterial nucleoprotein, a delayed cutaneous reaction, of slight extent, is often observed; the urticarial reaction, never. Under special conditions, treatment with a carbohydrate substance alone may result in the production of an immediate reaction. Are these new reactions temporary or permanent? How long can they be demonstrated in the animal or in the patient? Mote and Jones [13] followed their original patients for two years and found that with the passage of time the urticarial reaction observed at the height of the response fades off slowly until all that is left is a small, red, inflammatory, tuberculin-like response to the test dose. Simultaneously, the antibodies disappear slowly from the serum in corresponding fashion. This, in itself, is some evidence that the relation between the delayed inflammatory reaction and the immediate urticarial reaction depends on a quantitative rather than a qualitative basis.

Stevens and Jordani [14] have studied the reactions of asthmatic patients to various bacterial substances injected intracutaneously. In their patients the findings were much the same as in the experimental animals, except perhaps that in the patients the individual variations were greater. Immediate and delayed reactions occurred at the same time and to the same organism. More commonly, however, the nucleoprotein of one culture showed a delayed reaction while a similar preparation from another showed an immediate response. The authors studied also the duration of their tests and made the interesting observation that when once the tendency to give an immediate or delayed reaction was acquired, a similar response was obtained when the reaction was elicited at a later period. This fact fits in with the clinical

13. Mote, John R., and Jones, T. Duckett: The Development of Foreign Protein Sensitization in Human Beings, J. Immunol. **30**:149, 1936.

14. Stevens, F. A., and Jordani, L.: Reactions to Intracutaneous Injections of Nucleoproteins of the Upper Respiratory Pathogenic Bacteria in Asthmatic Patients, J. Allergy **7**:443, 1936.

observation that in many chronic diseases the reactions to new and recurrent attacks are much like the old reactions. Thus, in rheumatic fever a new cold will cause a new flare-up in the joints, whereas in asthma a new cold will cause bronchospasm. Incidentally, Krause [15] observed some time ago that a new attack of bronchitis is likely to begin in precisely the same part of the lung as the former attack. In allergy, one speaks of shock tissues in the effort to explain why it is that of two subjects sensitive to pollen, one will have hay fever and the other asthma. Obviously, the differences depend on changes in the tissue reactivity of certain areas.

Swift and Schultz [16] have worked on the synergic effect of two substances affecting the animal at the same time. They have confirmed the findings of Burky that the capacity of beef lens extract to produce sensitiveness in rabbits is greatly enhanced if the extract is mixed first with staphylococcus toxin. Furthermore, the effect is observed even if the two substances are injected separately and perhaps with an interval of several hours between the doses. If the animal is immune to staphylotoxin, the toxin is neutralized in vivo, and the synergic effect is lost. Neutralization in the test tube, however, does not prevent the reaction. In other experiments Swift and Schultz [17] found that the addition of horse serum likewise increased the antigenicity of the lens extract, although to a less extent than did the addition of toxin. In discussing their observations, the authors state their belief that the toxin probably acts as a stimulant to the antibody-producing cell rather than makes a new combination with the antigen. That neutralized toxin will work as well as native toxin and that horse serum also is effective is interesting even though the reason is obscure.

The pneumococcus remains the favorite object of study, no doubt because its specific capsular substance is well defined and can be separated from the bacterial protein. The chemical methods of this procedure have been revised and improved by Heidelberger and his co-workers.[18]

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15. Krause, A. K.: Chronic Pulmonary Infections in Childhood, Ann. Int. Med. **4**:1424, 1931.

16. Swift, H. F., and Schultz, M. P.: Studies in Synergy: The Synergic Action of Staphylotoxin and Beef Lens Extract in Rabbits, J. Exper. Med. **63**:703, 1936.

17. Swift, H. F., and Schultz, M. P.: Studies in Synergy: Synergic Stimulating Effect of Hypersensitivity to Foreign Protein and to Bacteria, J. Exper. Med. **63**:725, 1936.

18. Heidelberger, M.; Kendall, F. E., and Scherp, H. W.: The Specific Polysaccharides of Types I, II and III Pneumococcus: A Review of Methods and Data, J. Exper. Med. **64**:559, 1936.

Harley [19] has studied the relationship of allergy, anaphylaxis and immunity to pneumococci and has found another factor in the technic. Treatment with virulent S forms containing the soluble specific substance will prepare the animal so that it will react later to cutaneous tests with the carbohydrate. On the other hand, treatment with avirulent R forms does not have such an effect, although in this case a sensitiveness to the somatic P fraction can be demonstrated. Treatment with the whole vaccine results in responses which are variable, because obviously the material used is a mixture. Harley's article contains a number of interesting charts.

The mechanism of desensitization in anaphylaxis has been studied by Morris.[20] Long ago, Richard Weil [21] pointed out that passively sensitized guinea-pigs can be protected against shock by an excess of antibody, and Dale and Kellaway [22] demonstrated that a reaction of the sensitized uterus can be prevented by adding antibody to the bath. Morris repeated these old experiments but could not confirm them. After the treatment of sensitized animals with immune serum, the reactivity was reduced a little but not much. Furthermore, Morris showed that some protection could be obtained by nonspecific means, with salts and lipids and with foreign serum which was nonspecific. This protection was temporary, and soon sensitiveness reappeared, no doubt because of the persistence of traces of antigen in the original sensitizing serum. She argues that if desensitization was due to the saturation of cellular antibodies by a sublethal dose of antigen, then additional antibodies should resensitize the animal. The fact is, however, that attempts to resensitize were ineffective. Guinea-pigs passively sensitized with antipneumococcus horse serum were desensitized with the bacterial carbohydrate substance and then were given a supposedly shocking dose of normal horse serum. Nothing happened. The cellular antibody was not blocked. In the reverse experiments, Morris could show that animals passively sensitized with the same antipneumococcus serum and then desensitized with horse serum could withstand multiples of the fatal dose of the pneumococcus carbohydrate. Their reactivity had been reduced so that allergy was no longer important, but their resistance to infection was still at a high level. In spite of the fact that

19. Harley, D.: Pneumococcal Allergy, Anaphylaxis and Immunity, J. Path. & Bact. **41**:491, 1935.

20. Morris, Marion C.: The Relation Between Antianaphylaxis and Antibody Balance: I. The Role of Excess of Circulating Antibody in Hypersensitiveness, J. Exper. Med **64**:641, 1936; II. The Effect of Specific Desensitization upon Resistance to Infection and upon Antibody Balance, ibid. **64**:657, 1936.

21. Weil, Richard: Anaphylaxis, J. M. Research **30**:299, 1914.

22. Dale, H. H., and Kellaway, C. H.: Anaphylaxis and Immunity in Vitro, J. Physiol. **54**: cxliii, 1921.

the animals had been desensitized, a different test showed that the antibody content was not depleted. In these experiments dealing with carbohydrate and the immediate reaction to it, it appears that desensitization is not concerned with a reduction in antibody but depends on some other change, a nonspecific one, in the animal. In studying the disappearance of a reaction to the tuberculin test during fever, Pilcher [23] found that the reaction to the cutaneous test with codeine, which is positive in most normal persons, became negative during the fever and the rash of measles and scarlatina. The liberation of H substance had induced a refractoriness to whealing.

Mills and Dragstedt [24] made an attempt to produce a blockade of the reticulo-endothelial system with india ink, but in spite of this treatment it was easy to sensitize the animals to horse serum and later to cause anaphylaxis in them. Incidentally, Gernez [25] had the interesting idea of mixing serum with fatty substances in order to delay absorption. Mixtures of horse serum with hydrous wool fat or olive oil resulted in sensitization as usual and in comparable doses, but when sensitized animals were treated with the mixture subcutaneously and then several hours later were given a fatal dose of horse serum intravenously, half of them survived. Specific desensitization had been accomplished to some extent, showing that the oil had delayed the absorption. In considering experiments on anaphylaxis in guinea-pigs, the findings of Zinsser and Enders [26] are interesting. The authors could show that in the passive anaphylaxis experiment the time factor is not necessary. If the antibody and the antigen are both given intravenously, reactions will occur even though the two materials are injected at the same time; indeed the antibody may be injected some time after rather than before the antigen. However, this "reversed" passive anaphylaxis can be demonstrated only in certain breeds of guinea-pigs.

A little more light has been thrown on the background of allergy. It is conceivable that a vitamin deficiency could explain the incidence of clinical hypersensitiveness. Hochwald [27] studied the antiallergic

23. Pilcher, J. D.: Local Skin Reactions in Measles and Scarlet Fever in Relation to the Intracutaneous Tuberculin Reaction, Am. Rev. Tuberc. **31**:568, 1935.

24. Mills, Moore A., and Dragstedt, Carl A.: The Reticulo-Endothelial System and Anaphylaxis in the Dog, J. Immunol. **31**:1, 1936.

25. Gernez, C.: Attempts at Anaphylactic Sensitization and Desensitization of Guinea-Pigs by Mixtures of Serum and Lanolin (Hydrous Wool Fat), Compt. rend. Soc. de biol. **120**:186, 1935.

26. Zinsser, H., and Enders, J. F.: Variations in the Susceptibility of Guinea Pigs to Reversed Passive Anaphylaxis, J. Immunol. **30**:327, 1936.

27. Hochwald, A.: Antiallergic Properties of Vitamin C, Zentralbl. f. inn. Med. **56**:769, 1935.

properties of vitamin C and found that when 100 mg. of cevitamic acid was given to sensitized guinea-pigs a few minutes before the shocking dose, 18 of 29 animals had no symptoms. However, if the vitamin was given from two to four hours beforehand, no protection resulted. In other experiments, Hochwald found that treatment with glutathione shortly before the shocking dose also gave protection. Since the short interval of time is so important, the author concludes that protection of this sort cannot depend on vitamin storage but must be based on a mechanism similar to that of protection which follows the injection of various colloidal substances.

Solomonica,[28] working with vitamin C, obtained different results. In his work the time relation was different. When his animals were given doses of vitamin C subcutaneously prior to and during the sensitizing period, many of them survived. If, however, the doses were given during the last two weeks or only shortly before shock, the protection was much less. Solomonica's experiments were suggested by the observation that such endocrine preparations as anterior pituitary extracts and estrogenic substances seemed to inhibit anaphylactic shock, and he thought that the reasons might depend on the known fact that each of these preparations contains quantities of vitamin C.

Comparative studies of the rat and guinea-pig have long been contemplated because of the striking contrast in the immunologic behavior of the two animals. Pratt[29] was successful in producing symptoms of anaphylaxis in white rats, but none of his animals died, and all efforts to demonstrate specific reactions in the isolated uterus were unsuccessful.

Granted an allergic animal, how does sensitization develop? Ten years ago Matthew Walzer[30] describe an observation which is of real importance in suggesting a method of approach to a better knowledge of the physiology of the absorption of protein. He presented evidence that under certain circumstances protein can be absorbed unchanged into the blood stream. Since Walzer's first demonstration, it has been found that if small doses of serum from highly sensitive patients are injected into the skin of normal human recipients, according to the method of the Prausnitz-Küstner experiment, specific reactions can be produced in the spot of injection by treatments of three kinds: 1. Walzer fed the antigen (egg white or fish) to a fasting subject. 2. L. N.

28. Solomonica, B.: Vitamin C and Anaphylactic Shock in Guinea Pigs, J. Immunol. **31**:209, 1936.

29. Pratt, Henry N.: Studies of Anaphylaxis in the Albino Rat with Reference to Diet and Histamine, J. Immunol. **29**:301, 1935.

30. Walzer, M.: A Direct Method of Demonstrating Absorption of Incompletely Digested Proteins in Normal Human Beings, J. Immunol. **11**:249, 1926.

Gay [31] injected the antigen (ragweed) subcutaneously. 3. M. B. Cohen [32] used inhalation of the antigen (ragweed) in the form of crude dry pollen. In each case there was a flare-up in the passively sensitized skin. These experiments were described in the review of the literature of 1935. They are interesting partly because they point to a common principle in the production of allergic symptoms following contact with the allergen and partly because they suggest that the antigen itself—even in spite of being in such an enormous molecule as egg globulin—is absorbed unchanged into the blood stream. Walzer [33] has recently published his seventh paper on this problem; in it he shows that when the stomach is hyperacid, the appearance of the cutaneous reaction is delayed for from an average of seventeen minutes to twenty-four minutes. Alexander, Shirley and Allen [34] have investigated the route by which native protein can enter the blood. To dogs that had fasted for twenty-four hours they fed egg white in moderate doses, and three hours later they killed the animals with ether. Using rabbit antiegg serum of high potency, they could demonstrate a positive reaction to the precipitin test for the antigen (egg) in the lymph and in the systemic blood but not in the portal blood. Furthermore, both the lymph and the systemic blood caused reactions in isolated uteri of sensitized guinea-pigs and also in human skin passively sensitized with the serum of patients sensitive to egg. Alexander concludes that the absorption of the ingested protein is by way of the thoracic duct. Somewhat in line is the observation by Marks [35] that a positive reaction to the test for egg white in the urine, also by means of highly potent antiegg serum, is obtained in less than 20 per cent of patients with a normal alimentary tract but in 75 per cent of patients afflicted with active peptic ulcer. The results are so striking that the author advises the test as an additional method of diagnosis in gastric disease! The conclusion is hard to correlate with that of Walzer.

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31. Gay, L. N.: The Passive Transfer of Hypersensitiveness (Local and Contralateral Passive Transfer Experiments), Bull. Johns Hopkins Hosp. **40**: 270, 1927.

32. Cohen, M. B.; Ecker, E. E.; Breithart, J. R., and Rudolph, J. A.: The Rate of Absorption of Ragweed Pollen Material from the Nose, J. Immunol. **18**:419, 1930.

33. Walzer, M., and Gray, I.: Studies in Absorption of Undigested Protein in Human Beings: VII. Absorption of Unaltered Protein Introduced by Duodenal Tube into the Abnormal Gastro-Intestinal Tract, J. Allergy **8**:81, 1936.

34. Alexander, H. L.; Shirley, K., and Allen, D.: The Route of Ingested Egg White to the Systemic Circulation, J. Clin. Investigation **15**:163, 1936.

35. Marks, M. B.: Permeability to Egg Albumin in Peptic Ulcer: Possible Test for Activity of Peptic Ulcers; Preliminary Report, Am. J. Digest. Dis. & Nutrition **3**:41, 1936.

CHEMISTRY OF SENSITIZATION

The chemistry of sensitization with nonbacterial substances has been developed further. Landsteiner and Jacobs [36] have published three papers on the sensitization of animals with simple chemical compounds. In a series of experiments they have shown that artificial sensitiveness can be produced in rabbits by a variety of substances having a relatively simple chemical structure, the requirement being that these substances must be combined with protein. After sensitization the reaction can be demonstrated by applying the substance alone either by injection or by painting it on the unbroken skin. Such experiments are successful according as the chemical structure of the substance permits of its combination with proteins. Experiments with urushiol, which is contained in lacquer, showed a close relation between the sensitizing power and the ability of the substance to make substitution compounds with aniline. Dinitro and trinitro compounds have this ability, but dichloronitro compounds, which are already saturated, do not react. In the third paper the authors report on anaphylaxis induced by arsphenamine. When the drug was used in its original and unneutralized form to sensitize guinea-pigs by two intradermal doses, a later treatment given intravenously resulted in anaphylactic shock in over half the animals. Thus, there is evidence that the development of sensitiveness depends on the ability of the particular substance to form combinations with protein, that is to say, its own stability.

Meantime, Caulfeild [37] has made a great advance by showing that when potassium alum is added to pollen extract a suspension of the flocculent precipitate can induce anaphylactic sensitiveness when injected into guinea-pigs. Whether this alum has a chemical effect or whether the results depend merely on a physical change is a question for future study.

Somewhat similar is the finding of Spain and Newell [38] that when house dust is filtered through cellophane under great pressure, the filtrate is inert whereas the residue remains active. In this instance also, the increase of activity depends on a physical change. Incidentally, the activity of the fractions seemed to be proportional to the amount of nitrogenous material precipitable by trichloro-acetic acid. There was no correspondence between the degree of activity and the amount of

36. Landsteiner, K., and Jacobs, J.: Studies on the Sensitization of Animals with Simple Chemical Compounds, J. Exper. Med. **61**:643, 1936; II, ibid. **64**:625, 1936; III. Anaphylaxis Induced by Arsphenamine, ibid. **64**:717, 1936.

37. Caulfeild, A. H. W.; Brown, M. H., and Waters, E. T.: Alum as an Adjuvant in Sensitizing Guinea Pigs to Ragweed Pollen (Ambrosia Artemisiifolia), J. Allergy **7**:451, 1936.

38. Spain, W. C., and Newell, J. M.: Ultrafiltration of House Dust Extracts, J. Allergy **7**:134, 1936.

nitrogen precipitable by phosphotungstic acid. Osgood and Hubbard [39] have come to a similar conclusion in their claim that precipitation with trichloro-acetic acid provides a better measure of skin test activity in extracts of ragweed pollen.

CLINICAL ALLERGY

Diagnosis.—The diagnosis of the exciting cause of symptoms by means of cutaneous tests is still a dramatic procedure. However, as knowledge increases these tests lose some of their glamour. Alexander [40] recites the difficulties. He explains that localized allergy is the rule rather than the exception and asks:

> Need we always expect that when the shock organ is the lung or the nose or perhaps the blood vessels in the deeper layers of the skin (urticaria) the skin will also and always be sensitive sufficiently to reveal a positive skin test? Is it surprising that patients are clinically sensitive even though their skin tests are negative?

The fact remains that this discrepancy is always hard to prove by experiment, even though clinically the demonstration seems easy, as when the elimination of some food or dust relieves the symptoms. Meantime, the contrary difficulty is much more common and is easy to demonstrate. Positive reactions to cutaneous tests with no accompanying clinical symptoms are a common finding.

In a study of 32 employees in a bakery Colmes and his associates [41] found that 6 men showed a positive cutaneous reaction to wheat, but that only 2 of them had symptoms of sensitivity. The difference between the development of a positive reaction to a cutaneous test and the development of symptoms is real, but whether it represents more than a quantitative variation is uncertain.

In normal persons positive reactions to cutaneous tests made with routine allergens are common. In his review of the mechanism of cutaneous tests, Walzer [5] says that he is disturbed by the large number of positive results obtained in normal persons as reported in the literature and suggests that either the technic is faulty or the subjects are truly allergic but with a low degree of reactivity. Formerly, Simon and I [42]

39. Osgood, Howard, and Hubbard, Roger S.: Skin Exciting Activity of a Ragweed Pollen Extract as Measured by Its Content of Three Nitrogen Fractions, J. Allergy **7**:112, 1936.

40. Alexander, H. L.: Interpretation of the Skin Test Used in Allergic Disorders, Journal-Lancet **56**:131, 1936.

41. Colmes, A.; Guild, B. T., and Rackemann, F. M.: Studies in Sensitization, J. Allergy **6**:539, 1935.

42. Rackemann, F. M., and Simon, F. A.: Technic on Intracutaneous Tests and Results of Routine Tests in Normal Persons, J. Allergy **6**:111, 1935.

noted positive reactions in 50 per cent of normal persons. Now, Grow and Herman [43] report positive reactions in 55 per cent of 150 normal persons. Most of the reactions in our series were to kapok, cotton, feathers and house dust; and as H. N. Pratt suggested in the course of a conversation, why should it not be that many, if not all, persons have a tendency to become slightly sensitive to those substances to which they are exposed in some quantity every day? The extracts are not irritating, there are plenty of normal controls and the differences between the reactors and the controls are definite. Pratt's suggestion is interesting and finds support in the observations of Salén and Juhlin-Dannfelt.[44] These authors tested 432 persons belonging to different occupational groups and found that the presence of positive reactions to cutaneous tests corresponded closely with the respective occupations. Bakers reacted to wheat but not to horse dander; grooms reacted to horse dander and not to wheat. The idea fits in with the well known principle that children become sensitive to foods while adults become sensitive to dusts. O'Keefe [45] presents new figures on this point. Similarly, Parlato [46] points to the great frequency of positive reactions to tests with extracts of raw silk—of 166 allergic subjects, 33 per cent reacted to silk; whereas of 102 nonallergic subjects, 27 per cent reacted. Note that at least two thirds of the subjects showed no reaction. Pratt [47] finds that 79 per cent of children who have perennial asthma react to house dust.

The leukopenic index which Vaughan has studied with such enthusiasm has been doubted, and an editorial [48] in *The Journal of the American Medical Association* points out that under normal conditions the total leukocyte counts may show even wider fluctuations than do the counts in Vaughan's curves. The editorial includes a good bibliography. In the meantime, Rinkel [49] has found that Vaughan's method is of practical value. He found that postcibal leukocytosis was associated with foods not producing symptoms, whereas leukopenia was

43. Grow, Max H., and Herman, Nathan B.: Intracutaneous Tests in Normal Individuals, J. Allergy **7**:108, 1936.

44. Salén, E. B., and Juhlin-Dannfelt: The Occurrence of So-Called Latent Allergy, Acta med. Scandinav. **86**:505, 1935.

45. O'Keefe, Edward S.: An Analysis of Three Hundred Cases of Asthma in Children, New England J. Med. **214**:62, 1936.

46. Parlato, Salvatore J., and Swarthout, G.: A Study of the Silk Allergen, J. Allergy **5**:505, 1934.

47. Pratt, Henry N.: House Dust Hypersensitivity in Perennial Asthma of Childhood, J. Allergy **8**:60, 1936.

48. The Leukopenic Index and Food Allergy, editorial, J. A. M. A. **106**:1988 (June 6) 1936.

49. Rinkel, H. J.: Leukopenic Index in Allergic Diseases, J. Allergy **7**:356, 1936.

associated with symptoms. With this method, in several cases intractable asthma was cleared up promptly when the leukopenic index was used as an adjunct to other tests.

When all is said and done, the fact remains that the clinical history is the one important method in the diagnosis of the cause of symptoms in patients with clinical allergy. Recently, I [50] have described the "tricks" in history taking.

The results of cutaneous tests in infectious diseases with specific bacterial products deserve study because these diseases represent a relatively pure type of sensitization. In trichinosis, for example, the original observations of Bachman,[51] that the edematous reaction often with hemorrhage is easily developed in rabbits infected with Trichinella, has been studied in detail by Augustine and Theiler,[52] as described in previous reviews. Now comes a paper by Goldschlager [53] which confirms these reports and stresses the diagnostic importance of the immediate cutaneous reaction to an extract of trichinellas and which, as expected, develops at the same time that precipitins first appear in the circulating blood.

The Frei test for lymphogranuloma venereum is similar in general, but this test is based on a reaction of the delayed inflammatory type. Gray and his associates [54] applied it to 790 patients in St. Louis and found positive results in 3.4 per cent of the white population and in 40 per cent of the colored population. However, many of the subjects who showed a positive reaction revealed no clinical manifestation of the disease. Similar is the report by Cole and Levin [55] on the intradermal reaction for chancroid. Like the Frei test, this new chancroid test is specific; the reaction is delayed and inflammatory. This test and the Frei test, too, may show positive results for many years after the disease has passed.

The relation between allergy and diabetes is said to be antagonistic, as though insulin and epinephrine counteracted each other. Among

50. Rackemann, Francis M.: History Taking in Allergic Diseases, J. A. M. A. **106**:976 (March 21) 1936.

51. Bachman, G. W.: Intradermal Reactions in Experimental Trichiniasis: Preliminary Report, J. Prev. Med. **2**:169 and 513, 1928.

52. Augustine, D. L., and Theiler, Hans: Precipitins and Skin Tests as Aids in Diagnosing Trichinosis, Parasitology **24**:60, 1932.

53. Goldschlager, A. I.: Trichinosis: A Report of Eight Cases with Skin and Precipitin Tests, Ann. Int. Med. **8**:939, 1935.

54. Gray, S. H.; Hunt, G. A.; Wheeler, P., and Blache, J. O.: Lymphogranuloma Inguinale: Its Incidence in St. Louis, J. A. M. A. **106**:919 (March 14) 1936.

55. Cole, H. N., and Levin, E. A.: The Intradermal Reaction for Chancroids with Chancroidal Bubo Pus, J. A. M. A. **105**:2040 (Dec. 21) 1935.

1,240 diabetic patients König [56] found only 3 instances of this type. Wilmer [57] has claimed that allergic subjects can utilize more sugar than normal subjects (their curve for sugar is lower). MacQuiddy, McIntyre and Koser [58] found no difference in the level of the blood sugar during fasting between normal subjects and allergic subjects. Meantime, however, the injection of dextrose intravenously has been shown by many authors to be an important therapeutic adjunct in patients with intractable asthma. Conversely, Wegierko [59] has treated 40 patients by means of insulin shock, giving them 40 units of insulin before breakfast, preferably during an attack of dyspnea from the asthma. He observed that insulin shock stopped the attack of dyspnea.

HAY FEVER

The mechanism of treatment remains obscure. Last year Cooke, Barnard, Hebald and Stull [60] showed that when the blood serum of a patient with hay fever was obtained before treatment and then mixed and incubated with pollen extract (ragweed) and the mixture was then injected into the skin of a normal subject, a positive reaction resulted, and forty-eight hours later a test of this site showed a negative Prausnitz-Küstner transfer reaction. The transferring antibody in the serum had been neutralized by the ragweed so that it was no longer active. When, however, the same patient was treated successfully with pollen extract, a mixture of his serum with ragweed resulted in negative reactions after the preliminary injection into the normal subject, and the later test with ragweed then gave positive results. These findings were interpreted as evidence that in the course of treatment a new antibody was developed which had the power to prevent the union of antigen and antibody. In the serum after treatment the antibody was left free to sensitize the sites in the normal subject. If these observations can be repeated by other workers, they are, of course, of great importance.

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56. König, F.: Concurrence of Diabetes Mellitus and Bronchial Asthma, Med. Klin. **31**:545, 1935.

57. Wilmer, H. B.; Miller, M. M., and Beardwood, J. T.: Recent Advances in the Diagnosis and Treatment of Allergic Disease, with Special Reference to Glucose Tolerance and Metabolism, South. M. J. **29**:197, 1936.

58. MacQuiddy, E. L.; McIntyre, A. R., and Koser, Don: Blood Sugar Studies in Hay Fever and Asthma, J. Allergy **7**:471, 1936.

59. Wegierko, J.: Favorable Influence of Hypoglycemic State Following Administration of Insulin on Evolution of Bronchial Asthma: Caces, Presse méd. **43**:1379, 1935; Treatment of Bronchial Asthma by Insulin Shocks, ibid. **44**:731, 1936.

60. Cooke, R. A.; Barnard, J. H.; Hebald, S., and Stull, A.: Serological Evidence of Immunity with Coexisting Sensitization in a Type of Human Allergy (Hay Fever), J. Exper. Med. **62**:733, 1935.

Meantime, Wagner and I [61] have made a study of the crossed reactions between the pollens of different grasses. Cutaneous sites in normal recipients were passively sensitized with the serum of those patients who were sensitive to a number of grass pollens at the same time, and on the following day these several sites were desensitized by repeated doses of one grass and then tested with another grass. In many instances this later test gave a negative result—a crossed relationship could be demonstrated; but the relationships were not constant, and it was concluded that pollens contain both a specific factor and a group factor.

In another study [62] it was desired to throw light on the mechanism of desensitization by repeated treatment of single sites in patients who had hay fever and were actively sensitive. Repeated treatment of this sort did result in desensitization, but when the strength of the extract used was increased, new reactions occurred. Furthermore, if a day or two was allowed to intervene before the next treatment, the subsequent injection was likely to give a positive reaction. To us it was clear that desensitization of this kind was merely a quantitative change and was only temporary.

The perennial treatment of pollen allergy has many adherents. Peshkin,[63] however, believes that preseasonal treatment is still satisfactory. However, there are patients who do badly when the pollen extract is given shortly before the season and then are much better when in another year the pollen extract is given in regular monthly doses. More direct is the evidence presented by Vander Veer,[64] in which he shows that in a large series of cases the results with perennial treatment were better on the whole, although the percentage figures show that the amount of improvement was not great. Levin [65] studied the effect of massive doses of pollen extract on the size of the cutaneous reaction and found that it became negative in 14.9 per cent of cases. Sometimes clinical relief occurred without much change in the cutaneous

61. Rackemann, F. M., and Wagner, H. C.: The Desensitization of Skin Sites Passively Sensitized with Serum of Patients with Hay Fever: Crossed Reactions of Different Pollens; the Variations in the Recipient, J. Allergy **7**: 319, 1936.

62. Wagner, Harold C., and Rackemann, F. M.: Studies in Hay Fever: Specific Desensitization of Skin Sites in Actively Sensitized Persons, J. Allergy **7**:543, 1936.

63. Peshkin, M. M.: Critique of the Perennial Treatment of Pollen Allergy, J. Allergy **7**:477, 1936.

64. Vander Veer, Albert: The Relative Merits of Seasonal and Perennial Treatment of Hay Fever, J. Allergy **7**:578, 1936.

65. Levin, Samuel J.: The Effect of Massive Pollen Therapy on Skin Test Sensitivity, J. Allergy **8**:26, 1936.

reactivity. Results with pollen treatment are given by Ellis,[66] who stresses the use of mixtures of extracts made up according to the degrees of sensitiveness to different pollens. Of 143 patients, 40 per cent were completely relieved, and another 30.8 per cent secured marked relief.

Ionization treatment of hay fever has given disappointing results. Ramirez [67] observed 75 patients who received this treatment; in every case the treatment was a failure. Bernheimer [68] points to the risk of complications from a procedure of this sort. Vistreich [69] suggests the application of phenol to the nasal mucosa, claiming over 90 per cent relief in 75 per cent of 28 cases. For a time after the treatment, the mucosa was less sensitive to the application of dilutions of pollen, but the time was short.

Hodgson [70] gives a botanic survey of the island of Bermuda. Dwarf ragweed is scarce. The grass group occurs in insignificant amounts. It is Bermuda cedar pollenating in March which causes most of the trouble on the island.

ASTHMA

The mechanism of an attack of asthma is not yet understood. Walzer [71] reviews the arguments for the theory that the attack depends on spasm of the bronchial muscles and for the other theory that edema of the mucous membrane is responsible. The present evidence favors the latter theory strongly. Edema is the characteristic lesion in other manifestations of allergy as well as in the local allergy produced passively. Other findings support the edema theory. At autopsy the plugs of sticky material in all the smaller bronchi are the characteristic findings, as Wilmer and his associates [72] describe once more and as I have seen repeatedly in fatal cases. Hypertrophy of the bronchial glands is a common finding, and Dr. Mallory will describe it soon. This

66. Ellis, R. V.: Results Obtained in Treatment of Hay Fever with Pollen Extracts, Minnesota Med. **19**:507, 1936.

67. Ramirez, M. A.: Disappointing Results from the Ionization Treatment of Hay Fever, J. A. M. A. **106**:281 (Jan. 25) 1936.

68. Bernheimer, Leopold B.: Zinc Ionization in Nasal Allergy, J. A. M. A. **106**:1980 (June 6) 1936.

69. Vistreich, F.: The Effect of Intranasal Phenol Application in Hay Fever: Quantitatively Studied by a New Intranasal Swab Test with Pollen Extracts, Laryngoscope **46**:717, 1936.

70. Hodgson, H.: Report of Botanical Survey of Bermuda, New York State J. Med. **35**:27, 1935.

71. Walzer, M.: The Mechanism of the Paroxysm in Bronchial Asthma, Journal-Lancet **56**:117, 1936.

72. Wilmer, H. G.; Eiman, J., and Miller, M. M.: Pathologic Picture in a Case of Essential Bronchial Asthma: Roentgen Findings Ante and Post Mortem, J. Allergy **7**:156, 1936.

glandular hypertrophy with the resulting dense exudate, containing mucus, fibrin and eosinophilic débris, is much more striking than is the evidence of hypertrophy of the muscles. During life the physical signs change rapidly from one portion of the lung to another, obviously because these same mucus plugs form and then loosen, now in this area, now in that. When the obstruction from the plug is partial, emphysema develops behind it, but when the plugging is complete, the corresponding area collapses.

Closely related to the changes in the mucosa of the bronchi are the changes in the mucosa of the nose and sinuses. The nasal sinuses are involved in a high percentage of all patients with asthma. The nasal quality of the voice, the irregular obstruction, the rhinorrhea and then the presence of polypi and the findings of sinuses dull on transillumination and in roentgenograms present a combination which goes with a story of chronic persistent asthma to make a clinical picture which is characteristic. The nature of the sinus disturbance is not clear. Evidence of a local infection is not always present—the pathologic picture is one of edema with eosinophilia and round cell infiltration (chronic inflammation of a special sort); and, as Weille [73] has shown, the trouble in any one sinus is capable of clearing without local treatment to that particular sinus. Presumably, the sinusitis represents a special form of "allergic reaction." Cameron [74] agrees with this theory. It may depend on some variety of chronic nerve stimulation and consequent overactivity of the mucous membrane, as Phillips [75] has suggested in a paper entitled "The Fifth, Ninth and Tenth Nerves in Bronchial Asthma." Lasowsky and his associates [76] describe "hyperergic inflammation in tissues" during brief stimulation of nerves. Cooke and Grove [77] show that the incidence of sinusitis increases with the increase of age at the time of onset. In 92 per cent of 248 cases of infective asthma it was an etiologic factor. In the authors' hands operative treatment gave good results in 70 per cent of 120 patients.

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73. Weille, Francis L.: Studies in Asthma: XVIII. The Surgical Treatment of Chronic Sinusitis in Asthma, J. A. M. A. **100**:241 (Jan. 28) 1933.

74. Cameron, J. A. M.: Part Played by Allergy or Sensitization as Factor in Predisposing Mucous Membrane of Nasal Passages and Paranasal Sinuses to Infection and Its Bearing upon Treatment of Disease of These Cavities, J. Laryng. & Otol. **50**:493, 1935.

75. Phillips, K.: The Fifth, Ninth and Tenth Nerves in Bronchial Asthma, Ann. Otol., Rhin. & Laryng. **45**:373, 1936.

76. Lasowsky, J. M.; Wyropajew, D. N., and Jurmann, M. N.: Hyperergic Inflammation in Tissues During Brief Stimulation of Nerves, Virchows Arch. f. path. Anat. **295**:334, 1935.

77. Cooke, R. A., and Grove, R. C.: Relation of Asthma to Sinusitis, with Special Reference to the Results from Surgical Treatment, Arch. Int. Med. **56**:779 (Oct.) 1935.

Weille [78] has had an extensive experience in the problem of the relation between the nose and throat and the asthma. A study of his end-results shows that of 100 sinus operations, ultimate cure was obtained in only 10 patients, although another 55 were markedly benefited. Tonsillectomy was performed on 36 patients—one was "cured," and in 24 the condition was improved. The extraction of abscessed teeth gave better results. Of 59 patients, 3 were "cured" and 36 were benefited. These particular results are long term results. A few patients were followed for only six months, but about four fifths of them were followed for at least a year, and two fifths were followed for over three years. The figures are disturbing, perhaps, but it must be remembered that treatment of this sort is directed at the result of a disease process and not at its cause.

An interesting novelty is the suggestion by Moruzzi [79] that asthma be treated by injecting the patient's serum into the nasal mucosa in daily doses of from 0.2 up to 1 cc. He treated 11 patients in this way—3 were relieved and 4 improved (he does not say how long they were followed up).

Cardiac Asthma.—Cardiac asthma is discussed by Ernstene and Knowlton.[80] The seizure usually depends on a sudden failure of the left ventricle, so common in older persons with advanced arteriosclerosis. Cardiac asthma may, however, occur also in younger persons who have mitral stenosis and then suffer a sudden increase in the heart rate and in the pulmonary congestion. Venesection as a mode of therapy deserves more attention.

It is a pleasure to read the report of Conybeare and Witts,[81] which emphasizes the changing character of asthma, the many different factors which enter into the cause of the attack and the recovery from it and, consequently, the ever present difficulty of determining the effect of treatment with true accuracy.

Specific Treatment of Asthma.—The specific treatment of asthma has received scant attention. Closely related, however, is the article by Fantus and Feinberg [82] on the therapy of reactions to horse serum,

78. Weille, Francis L.: Studies in Asthma: XIX. The Nose and Throat in Five Hundred Cases of Asthma, New England J. Med. **215**:235, 1936.

79. Moruzzi, D.: Intramucous Autoserum Therapy for Bronchial Asthma, Policlinico (sez. prat.) **42**:905, 1935.

80. Ernstene, A. C., and Knowlton, R. S.: Cardiac Asthma, Ohio State M. J. **32**:717, 1936.

81. Conybeare, E. T., and Witts, L. J.: A Criterion for the Treatment of Asthma, Guy's Hosp. **85**:138, 1935.

82. Fantus, Bernard, and Feinberg, S M.: The Therapy of (Horse) Serum Reactions: General Rules in the Administration of Therapeutic Serums, J. A. M. A. **107**:1717 (Nov. 21) 1936.

with the rules governing the administration of therapeutic serum. The technical procedures are explained carefully. A method of oral desensitization to common foods is described by Keston, Waters and Hopkins [83] and in their hands has been found to be effective, especially in the treatment of small children with chronic allergic eczema due to hypersensitiveness to food. The method consists essentially in a series of increasing daily doses.

Graeser and Rowe [84] present another article on the inhalation of epinephrine hydrochloride as a method for relief of asthma in children. This is of practical value, as I know from experience. Nowadays the special atomizer and the small bottle of 1 : 100 solution of epinephrine hydrochloride are put up together by the pharmaceutic house so that the outfit is neat, convenient and not too expensive. It is important, however, that the patient be carefully instructed in its use, for unless the bulb is squeezed at the beginning of inspiration the spray will not be inhaled deeply into the finer bronchi, and good results will not be obtained. Ellsworth and Sherman [85] describe a case in which the injection of epinephrine in an asthmatic patient resulted in tetany, which developed promptly after the relief of the bronchial spasm. The short interval suggested strongly that hyperventilation made possible by the epinephrine resulted in the washing out of carbon dioxide and the production of alkalosis and, consequently, tetany. The occurrence is another argument against the use of excessive doses of epinephrine. In the ordinary patient such a small quantity as 0.3 cc. of the solution is as effective as a larger amount, which often is followed by disagreeable by-effects, such as shivering, headache, pallor and tachycardia.

Nonspecific Treatment of Asthma.—Nonspecific therapy is widely used in asthma. Two important articles, one by Hektoen [86] and the other by Cecil,[87] on nonspecific protein therapy in general deserve careful attention. That nonspecific treatment does not act by stimulating the eosinophil cells is shown by Peshkin and Messer,[88] who found that

83. Keston, B. M.; Waters, I., and Hopkins, J. G.: Oral Desensitization to Common Foods, J. Allergy **6**:431, 1935.

84. Graeser, J. B., and Rowe, A. H.: Inhalation of Epinephrine Hydrochloride for Relief of Asthma in Children, Am. J. Dis. Child. **52**:92 (July) 1936.

85. Ellsworth, Read, and Sherman, William B.: Tetany in an Asthmatic Patient Following the Administration of Epinephrine, J. A. M. A. **106**:284 (Jan. 25) 1936.

86. Hektoen, Ludvig: Reactions to Nonspecific Protein Treatment of Infectious Diseases, J. A. M. A. **105**:1765 (Nov. 30) 1935.

87. Cecil, Russell L.: Nonspecific Protein Therapy, J. A. M. A. **105**:1846 (Dec. 7) 1935.

88. Peshkin, M. M., and Messer, William: Asthma in Children: XII. Influence of Specific and Nonspecific Treatment on the Differential Leukocyte Count; with Special Reference to the Eosinophils, Am. J. Dis. Child. **50**:1374 (Dec.) 1935.

a venom protein solution, which stimulates the eosinophils more than does milk, is not more effective in cases of asthma in children than are injections of milk.

Intractable Asthma.—The treatment of intractable asthma is always difficult. Balyeat and his associates [89] have had real success with the intratracheal injection of iodized poppy seed oil in doses of from 5 to 10 cc. instilled at intervals of from one to four weeks. In 35 of the 50 patients in whom poor results were obtained by allergic management, good results were finally obtained by the use of this method. The authors can demonstrate roentgenographically that when the bronchi are filled with a tough, sticky exudate the injected oil works its way below the exudate to float it upward and thus to close off the smaller tubes. In this way the mechanical factor dependent on the presence of the sticky mucus is modified. Anderson [90] also has used this method, and he claims that patients who have been treated by intratracheal injection of iodized oil have lost their clinical sensitiveness to former irritants. Furthermore, he finds the treatment safe and without danger, either immediate or remote, to the lungs. In my experience iodized oil persists for some time in the bronchi, as can be shown by repeated roentgenograms, and no doubt a series of lipoid granulomas are often produced. It may be, however, that even if granulomas are formed, they do little harm.

Histamine is recommended by Dzsinich,[91] who gave increasing doses to 15 patients with bronchial asthma and to 3 with urticaria—the maximum dose being 0.01 mg. Frequently, ten or twelve injections resulted in complete disappearance of the symptoms.

Dorsal sympathectomy has been tried by Levin,[92] who recommends the destruction of the rami either by injections of alcohol or by operative removal of the upper portion of the thoracic ganglionated trunk. In 75 per cent of 23 patients with severe asthma treated by this method complete relief was obtained.

Helium should be, at least theoretically, the ideal means for treating severe asthma. The size of the bronchial lumen is reduced by muscular spasm or by the formation of the sticky exudate and plug, and

89. Balyeat, A.; Seyler, L. E., and Shoemaker, H. A.: The Diagnostic and Therapeutic Use of Iodized Oil in Cases of Intractable Asthma, Radiology **24**:303, 1935.

90. Anderson, William: The Treatment of Bronchial Asthma by Intratracheal Injections of Iodized Oil, New York State J. Med. **36**:1151, 1936.

91. Dzsinich, A.: Histamine in Treatment of Allergic Conditions (Bronchial Asthma and Urticaria), Klin. Wchnschr. **14**:1612, 1935.

92. Levin, G. L. L.: The Treatment of Bronchial Asthma by Dorsal Sympathectomy, Direct and Indirect (Use of Alcohol), Ann. Surg. **102**:161, 1935.

anything which will increase the flow of air past the obstruction is to be recommended. A. L. Barach,[93] who originated the method of using helium, deserves great credit. In two new articles, illustrated by pictures and diagrams, he describes new refinements in the technic and the results of new studies on the physiologic effects and the clinical end-results. Briefly, these include decreases in the pulmonary ventilation, in the pulmonary pressure and in the length of expiration.

Prognosis.—The prognosis in asthma is generally good. Studies of end-results in patients with clinical allergy are conspicuous by their absence, and it is gratifying to find a paper by Leon Unger [94] on the results of treatment in 207 cases after a period of from one to thirteen years. Forty-five of his patients were "cured," and 104 were greatly improved. The figure of 21 per cent is interesting, because it is practically the same as the figure which I obtained in a follow-up of 1,074 patients in 1928. If other physicians whose methods of treatment are so well described would employ the same yardstick, the comparative results would be interesting and instructive.

Witts [95] considers the prognosis in asthma in an article which is along general lines and is full of common sense, but he does not present figures to define the end-results exactly.

ECZEMA

Sulzberger [96] has published several papers on the varieties of dermatologic allergy, discussing at the same time the problems of nomenclature and classification and, more recently, the medicolegal aspects. The patient who becomes sensitive to some occupational dust has two difficulties. First, his work has brought him into contact with the substance and the employer appears liable; but, second, he alone out of many other workers has shown symptoms—he has a constitutional sus-

93. Barach, A. L.: Use of Helium in Treatment of Asthma and Obstructive Lesions in Larynx and Trachea, Ann. Int. Med. **9**:739, 1935; The Effects of Inhalation of Helium Mixed with Oxygen on the Mechanics of Respiration, J. Clin. Investigation **15**:47, 1936.

94. Unger, Leon: Bronchial Asthma: Results of Treatment in Two Hundred and Seven Patients Under Observation for a Period Varying from One to Thirteen Years, J. Allergy **7**:364, 1936.

95. Witts, L. J.: Prognosis in Asthma, Lancet **1**:273, 1936.

96. Sulzberger, M. B., and Goodman, Joseph: Nomenclature, Definition and Classification of Allergy and Allergic Manifestations, M. Rec. **143**:17, 1936; Remarks on Definition and Classification in Certain Forms of Dermatologic Allergy, New England J. Med. **215**:330, 1936; The Relative Importance of Specific Skin Hypersensitivity in Adult Atopic Dermatitis, J. A. M. A. **106**: 1000 (March 21) 1936; Medico-Legal Aspects of Occupational Dermatoses, Am. J. Surg. **30**:531, 1935. Sulzberger.[4]

ceptibility, which is allergy, and for this the employer is not liable. In legal medicine the problem is real and is not limited necessarily to the cutaneous manifestations of clinical allergy.

A number of articles concern interesting cases. Brunsting and Williams [97] have collected the reports of 48 patients with ragweed dermatitis. Caulfeild [98] describes tulip fingers. Biederman [99] studied a truck driver who was sensitive to gasoline. The relation between his work and the occurrence of dermatitis was clearcut, and when he was tested by placing one arm over the open mouth of a bottle of gasoline, itching, redness and later blisters developed on the exposed sites, the reaction continuing for from twenty-four to forty-eight hours. A similar test on the doctor's arm gave negative results. Grolnick [100] has written two articles on the question of dermatitis due to adhesive plaster, describing the substitutes for adhesive plaster which can be used in making a patch test. Bonnevie and Genner [101] add a report of another patient with eczema due to the dyes in clothing. Hoffman and Rattner [102] found two children in whom eczema was caused by cod liver oil. Sulzberger [103] finds that itch mites of canary birds can cause dermatitis in human beings.

In all these cases the diagnosis depended primarily on the intelligent taking of the history, which suggested the proper selection of substances to be tested by the patch method.

Meantime, Field and Sulzberger [104] describe a patient who was evidently sensitized by the cutaneous tests. The fact indicates that the discrepancy of results may sometimes depend on the development of sensitiveness during the period of study.

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97. Brunsting, Louis A., and Williams, Donald H.: Ragweed (Contact) Dermatitis, J. A. M. A. **106**:1533 (May 2) 1936.

98. Caulfeild, A. H. W.: "Tulip Fingers," Ragweed Dermatitis, Canad. M. A. J. **34**:506, 1936.

99. Biederman, Joseph B.: A Case of Contact Dermatitis Produced at a Distance, J. A. M. A. **106**:2236 (June 27) 1936.

100. Grolnick, M.: Studies in Contact Dermatitis: I. Adhesive Plaster Dermatitis; Technics for Surface Testing on Patients Sensitive to Adhesive Plaster, J. Allergy **7**:341, 1936; II. Adhesive Plaster Dermatitis: Clinical and Immunologic Observations on Patients Sensitive to Adhesive Plaster, ibid. **7**: 556, 1936.

101. Bonnevie, P., and Genner, V.: Eczema Due to Dyed Clothing, Arch. Dermat. & Syph. **34**:220 (Aug.) 1936.

102. Hoffman, S. J., and Rattner, H.: Infantile Eczema from Cod Liver Oil: Report of Two Cases, J. A. M. A. **107**:494 (Aug. 15) 1936.

103. Sulzberger, M. B., and Kaminstein, I.: Avian Itch Mites as a Cause of Human Dermatoses: Canary Birds' Mites Responsible for Two Groups of Cases in New York, Arch. Dermat. & Syph. **33**:60 (Jan.) 1936.

104. Field, Hans, and Sulzberger, M. B.: Experiments in Poison Ivy Sensitivity, J. Allergy **7**:139, 1936.

FUNGI IN ALLERGY

Dermatologists have been greatly interested in the new approach to the diagnosis of diseases of the skin which the advance in the knowledge of allergy and of fungi has opened up in the last few years. Swartz [105] presents the essentials of the classification of fungi in his general article on their rôle in medicine. Pennington [106] has analyzed 155 cases of allergic dermatitis and found that sensitivity to fungi was involved in about 60 per cent and was the sole cause of trouble in 30 per cent. Thirty-three patients were treated with doses of fungus extract given intracutaneously. Of these, 21 were cured and another 6 were definitely improved. In some cases, however, other methods of treatment, including removal of test-positive substances, were employed.

A certain type of eczema depends on a specific cause which is carried to the skin by the blood stream. In this type the method by which the offending substance reaches the blood makes little difference. For example, in a child with typical infantile eczema, egg is absorbed from the gastro-intestinal tract. In other cases the allergen may be absorbed by inhalation through the lungs. Dust can cause eczema which, like hay fever and asthma, may come and go with changes in environment. The new knowledge of fungus spores in the air and their relation to inhalant allergy of all sorts is of practical importance. An increase in the knowledge of molds will be desirable.

Lamson and Rogers [107] found that 12 per cent of 1,259 patients with asthma and hay fever showed a positive reaction to cutaneous tests with molds, while Feinberg [108] found that 28 per cent of his patients with asthma and hay fever reacted to molds. In another paper Feinberg [109] presents charts showing the daily incidence of mold spores in the air and the relation between their number and the occurrence of symptoms in his patients. Underwood [110] has found that, even if molds are not the primary cause of trouble, an additional sensitiveness to them can make a bad condition worse.

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105. Swartz, J. H.: The Rôle of Fungi in Medicine, New England J. Med. **215**:322, 1936.

106. Pennington, Edna S.: An Evaluation of the Relative Role of Fungi (Trichophytin) and Other Allergens in Patients with Allergic Dermatoses, South. M. J. **29**:407, 1936; Trichophytin and Monilia Extracts in Allergic Dermatoses, J. Allergy **7**:54, 1935.

107. Lamson, Robert W., and Rogers, Erving L.: Skin Hypersensitivity to Molds, J. Allergy **7**:582, 1936.

108. Feinberg, S. M.: Mold Allergy: Its Importance in Asthma and Hay Fever, Wisconsin M. J. **34**:254, 1935.

109. Feinberg, S. M., and Little, H. T.: Studies on the Relation of Microorganisms to Allergy, J. Allergy **7**:149, 1936.

110. Underwood, G. R.: Importance of Fungus (Alternaria) as Cause in Nebraska, Nebraska M. J. **20**:400, 1935.

The former observations of Cohen [111] have been confirmed by Wagner and myself [112] and the importance of fungi in their effect on various environmental substances is being better understood. When fibers of cotton or kapok which are new and unused are extracted, the fluid gives positive results to cutaneous tests in only a few patients. When, on the other hand, extracts are made of old, used material, a large proportion of the cutaneous reactions are found to be positive. That this change depends chiefly on the activity of fungi which grow on the vegetable fiber is shown in various ways. Conant, Wagner and myself [113] found numerous fungi in cultures of the stuffing in pillows, mattresses and furniture. Brown [114] filled flasks with new cotton fiber and then inoculated them with mold cultures. Cutaneous tests with extracts of the resulting mixture, however, gave negative results. My colleagues and I have made a similar study, which will be presented soon. We shall show, first, that sterilization by steam pressure of new vegetable fiber hinders the growth of molds on the fiber and, second, that the choice of molds is important, because whereas certain molds will grow well on certain substrates these same molds will not grow well on other substrates. In our experience it is possible to produce a good growth of molds in flasks full of new material and to show that after a time extracts of this growth often produce positive reactions in cutaneous tests. This new knowledge is of practical importance because the list of patients in whom asthma has been completely relieved by simple changes in bedding and furniture is considerable. In the meantime, that cutaneous tests made with fungus extracts are often associated with reagins has been demonstrated by Persons and Martin [115] and also by Cazort.[116]

URTICARIA

Hopkins and Kesten [117] have made a useful and practical list and classification of the varieties of urticaria, differentiating between acute and chronic forms and their causes, as well as between localized and

111. Cohen, Milton B.: Observations on the Nature of the House Dust Allergens, J. Allergy **6**:517, 1935.

112. Wagner, Harold C., and Rackemann, F. M.: Kapok, J. Allergy **7**: 224, 1936.

113. Conant, N. F.; Wagner, Harold C., and Rackemann, F. M.: Fungi Found in Pillows, Mattresses and Furniture, J. Allergy **7**:234, 1936.

114. Brown, Grafton T.: Hypersensitiveness to Fungi, J. Allergy **7**:455, 1936.

115. Persons, E. L., and Martin, D. S.: Passive Transfer Antibodies for Six Saprophytic Fungi in a Patient with Superficial Scaling Dermatosis, J. Clin. Investigation **15**:429, 1936.

116 Cazort, A. G.: The House Dust Antigen in Allergy, South. M. J. **29**: 1022, 1936.

117. Hopkins, J. G., and Kesten, B. M.: Urticaria: Etiologic Observations, Arch. Dermat. & Syph. **29**:358 (March) 1934.

generalized lesions. They recognize that in this, as in other varieties of allergy, the offending substance to which the patient is hypersensitive may enter the body through the respiratory tract and be distributed by the blood. In another group of patients the disease seemed to depend on a focus of infection, and the authors consider that urticaria from this cause may occur even in patients who have not an allergic predisposition.

DRUG ALLERGY

Drug allergy is receiving more and more attention, and clinicians are becoming aware of its increasing frequency. In considering the chemistry of hypersensitiveness, it was pointed out that those substances which are relatively unstable and which, therefore, combine easily with protein are also those substances to which a specific sensitiveness is often acquired. Perhaps it is for this reason that the modern development of many new drugs has sometimes led to trouble.

Benjamin and Biederman [118] describe a patient in whom agranulocytic leukopenia developed following the use of novaldin, which is a close relative of aminopyrine. Strauss [119] describes a patient who took a single tablet of peralga (another form of aminopyrine) and in whom collapse and severe asthma developed. Dinitrophenol caused asthma in a patient reported on by Noun.[120] Dameschek and Colmes [121] demonstrate a strongly positive cutaneous reaction when aminopyrine was mixed with protein (blood serum) and the mixture was used for a scratch test. Lichtenstein and Stillians [122] report the case of a young man with tuberculosis who received six intravenous injections of gold sodium thiosulfate and in whom exfoliative dermatitis developed which persisted for several months. Hudson [123] has described purpura haemorrhagica as due to a sensitiveness to compounds of gold and arsenic. During the illness patch tests with gold sodium sulfate gave positive results. Other patients with similar though less severe dermatitis also showed a positive reaction to a patch test with the drug.

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118. Benjamin, J. E., and Biederman, J. B.: Agranulocytic Leukopenia Induced by a Drug Related to Aminopyrine, J. A. M. A. **107**:493 (Aug. 15) 1936.

119. Strauss, M. G.: Allergy to Amidopyrine: Blood Studies Following Anaphylactic-Like Shock in a Patient, New England J. Med. **215**:177, 1936.

120. Noun, M. H.: Asthma from Dinitrophenol Sensitization (Case), J. Iowa M. Soc. **25**:610, 1935.

121. Dameshek, William, and Colmes, A.: The Effect of Drugs in the Production of Agranulocytosis, with Particular Reference to Amidopyrine Hypersensitivity, J. Clin. Investigation **15**:85, 1936.

122. Lichtenstein, M. R., and Stillians, A. W.: Results of Patch Tests with Gold Sodium Thiosulphate, Arch. Dermat. & Syph. **31**:758 (May) 1935.

123. Hudson, E. G.: Purpura Hemorrhagica Caused by Gold and Arsenical Compounds, Lancet **2**:74, 1935.

Martinaud [124] observed a patient who had a fatal attack of asthma during an attempt to produce local anesthesia of the nose with a solution of butyn.

Hypersensitiveness to substances of simple chemical structure may, however, occur. Gelfand [125] reports on a patient who was hypersensitive to arsenic and in whom marked generalized dermatitis developed after the application of a hair tonic and dandruff remover. Settle [126] had a patient who took two tablets of quinine sulfate and the next day had inflammatory lesions on the palms and on the tongue.

As Hunter [127] pointed out in his inclusive review of the literature published in 1935, there is, in almost all of these cases, a history of three distinct circumstances. First, the drug was taken for a considerable period without difficulty. Second, there was another considerable period during which the drug was not taken, and then, third, symptoms occurred promptly when the drug was taken again after the interval. In these cases there are sensitization and incubation that are entirely comparable to the anaphylaxis experiment.

Other special cases are described. Card [128] had a patient who worked in a chromium-plating factory and it was found that an attack could be provoked by the injection of 4 mg. of potassium dichromate. Parlato [129] studied a nun who had corneal ulcers caused by sensitiveness to the sachets used in the church vestments. She gave a marked reaction to cutaneous tests with orris powder. The frequency with which patients show a positive reaction to cutaneous tests with extracts of human tissues is described in an interesting paper by Simon and Ryder,[130] who found that extract of pituitary caused a reaction in a small percentage of subjects.

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124. Martinaud, M.: Fatal Attack of Asthma During Local Anesthesia by Washing Nasal Mucosa with Solution of Butyn: Case, Anesth. et analg. **1**: 199, 1935.

125. Gelfand, H. Harold: Hypersensitiveness to Arsenic: Dermatitis from Liquid Arvon, J. Allergy **7**:254, 1936.

126. Settle, R. O.: Dermatitis Medicamentosa Due to Quinine, J. A. M. A. **106**:1801 (May 23) 1936.

127. Hunter, F. T.: Agranulocytosis, New England J. Med. **213**:663, 1935. Kracke, R. R., and Parker, F. P.: The Relationship of Drug Therapy to Agranulocytosis, J. A. M. A. **105**:960 (Sept. 21) 1935.

128. Card, W. Ingram: A Case of Asthma Sensitivity to Chromates, Lancet **2**:1348, 1935.

129. Parlato, Salvatore, J.: Corneal Ulcers Due to a Common Allergen, Arch. Ophth. **14**:587 (Oct.) 1935.

130. Simon, Frank A., and Ryder, C. F.: Hypersensitiveness to Pituitary Extracts, J. A. M. A. **106**:512 (Feb. 15) 1936.

OTHER SYMPTOMS OF ALLERGY

Foster Kennedy [131] has listed a number of neurologic disturbances which may be attributable to allergy. Certain convulsive states and some forms of retrobulbar neuritis are in the list, as well as migraine. More interesting are the cases in which paralysis of certain nerves occurs after doses of foreign serum and perhaps represents a certain special form of serum disease. Hemiplegia has been described in this connection, and another patient with urticaria suffered a migrating type of paralysis which seemed to follow a migrating type of edema.

In close accord is the case report by Cutter,[132] of San Francisco, concerning a boy of 14 who stepped on a rusty nail in a barnyard. Three weeks later he visited a physician because of twitchings in various muscle groups for one day and inability to open his jaw. Within forty-eight hours he was given 125,000 units of tetanus antitoxin. Five days later he was given 15,000 units. After that increasing deafness developed, with noises in the ears and double vision. The symptoms lasted for about a month. It is surprising perhaps that this treatment with foreign serum given at the intervals stated did not result in an even more vital reaction.

Migraine.—Migraine is still a difficult problem. Some light has been thrown on its mechanism by Goltman,[133] who observed a young woman with headache severe enough to require cerebral exploration. Through a burr opening, Goltman could observe that during the aura there was spasm of the cerebral vessels, but with the onset of the headache he could see vascular dilatation develop, with edema of the brain. The clinical aspects of migraine are well described in a paper by Gordon,[134] who points out that allergy can be demonstrated as an important factor in only a relatively small proportion of cases. The treatment of migraine with ergotamine tartrate has been advocated and pursued by Lennox.[135] His recent experiences with the drug in 120 cases are presented. Relief from an attack was obtained in 107 cases.

Other Symptom Complexes.—Other complexes have been described as having an allergic basis—gout by Pasteur Vallery-Radot,[136] articular

131. Kennedy, Foster: Allergic Manifestations in the Nervous System, Tr. Am. Neurol. A. **61**:49, 1935.

132. Cutter, Richard D.: Auditory Nerve Involvement After Tetanus Antitoxin: First Reported Case, J. A. M. A. **106**:1006 (March 21) 1936.

133. Goltman, A. M.: The Mechanism of Migraine, J. Allergy **7**:351, 1936.

134. Gordon, A. H.: A Clinical Lecture on Migraine, New England J. Med. **213**:1017, 1935.

135. Lennox, W. G., and von Storch, T. J. C.: Experience with Ergotamine Tartrate in One hundred and Twenty Patients with Migraine, J. A. M. A. **105**: 169 (July 20) 1935.

136. Vallery-Radot, P., and Mauric, G.: Gout and allergie, Progrès méd., Oct. 12, 1935, p. 1631.

disease by Wellisch [137] and disorders of the gastro-intestinal tract, liver and gallbladder by Urbach [138]; but in none of the cases does the evidence for an allergic cause rest on a firm foundation. On the other hand, Lewin and Taub [139] describe a patient subject to recurrent attacks of synovitis which seemed to be due to the ingestion of English walnuts. Cohen [140] mentions periarteritis nodosa, having made the diagnosis in 2 cases of asthma before death occurred. He writes: "The diagnosis is not difficult if the clinician will . . . watch for symptoms and signs which may be explained on the basis of a temporary or permanent blood supply to any organ."

SUMMARY

The problems to which I referred in the review of two years ago are not yet solved. The function and purpose of the allergic reaction are being studied, and some attempt is being made to apply the results of laboratory experiments to patients, but there is still a long way to go. The increased understanding of tissue reactions is a step forward. Concerning the allergic subject, it is not yet clear that his variation from the normal depends on anything more than a quantitative change. Fortunately, however, the students of allergy are paying more attention to the patient as a whole. Studies of metabolism, of hormones and of food factors have been begun. Precise information on the mechanism of the production of symptoms, however, is still lacking. Surely there must be some reason for the prostration and illness associated with chronic intractable asthma. The whole subject is fascinating, partly because the field is large and the problems diverse and partly because any important results will lead to the benefit of a large number of persons who really suffer.

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137. Wellisch, E.: Allergic Components in Diseases of Joints, Wien. med. Wchnschr. **85**:935, 1935.

138. Urbach, E.: Allergic Disorders of Gastro-Intestinal Tract, Liver and Gallbladder, Rev. méd.-chir. d. mal. du foie **11**:116, 1936.

139. Lewin, Philip, and Taub, Samuel J.: Allergic Synovitis Due to Ingestion of English Walnuts, J. A. M. A. **106**:2144 (June 20) 1936.

140. Cohen, M. B.; Kline, B. S., and Young, A. M.: The Clinical Diagnosis of Periarteritis Nodosa, J. A. M. A. **107**:1555 (Nov. 7) 1936.

Book Reviews

By-Effects in Salvarsan Therapy and Their Prevention. By Dr. V. Genner. Price, 22 kroner. Pp. 360. Copenhagen: Levin & Munksgaard, 1936.

This monograph, compiled from the experience of the University Clinic of Dermatovenerology, at Copenhagen, assembles a mass of clinical data regarding arsenic intoxication during the treatment of syphilis. The entire subject, of course, is of great interest and has been widely studied; it must have been tedious work to gather together the very extensive literature which is reviewed, to assemble it properly and to add observations regarding it.

First, there is discussed the theoretical basis for arsenic intoxication; then there follow chapters on arsphenamine erythema, jaundice, albuminuria and what the author calls "paratherapeutic joint complaints." These chapters lead to a discussion as to how such uncomfortable by-effects of arsphenamine therapy may be avoided, especially by the use of a concentrated dextrose solution as a solvent for the arsphenamine. Finally the author pleads for individualization of antisyphilitic treatment; for, he claims, it is possible before treatment is begun to determine whether a patient is intolerant to arsphenamine and to plan a suitable individualized treatment so that he can receive adequate therapy without serious or permanent injury.

On the whole, the material of the book is well digested, so that the monograph should be useful as a work of reference not only to syphilographers but also to all clinicians who administer the various arsenicals.

Aparato respiratorio. By Doctores F. Martinez and Isaac Berconsky. Pp. 283. Buenos Aires: Ed. Ateneo, 1936.

This volume is an interesting and complete treatise on the respiratory system. It is in actuality a work on physical findings, in which the authors thoroughly cover the anatomy, physiology and pathology of the respiratory system, including the topography of the chest. In their volume they consider the mediastinum, pleura and diaphragm in separate chapters.

The printing is on excellent paper, and the entire contents are profusely illustrated with exceptionally clear figures. The chapters on topography and physical examination of the thorax are especially commendable. There is an excellently illustrated chapter on radiology.

In undertaking a work of this kind, the authors have succeeded in eliminating a large majority of the obsolete signs to which a work on physical diagnosis seems to be heir. The volume lends itself readily to teaching purposes. It is unfortunate that there is not a chapter on the heart and the great vessels.

Treatment in General Practice: The Management of Some Major Medical Disorders. [Articles Reprinted from the British Medical Journal.] Price, $3.50. Pp. 260, with 6 illustrations. New York: Paul B. Hoeber, Inc., 1936.

This series of articles on treatment arouses no enthusiasm in the reviewer. The discussion is superficial, full of outworn "practical" advice and burdened with complicated, old-fashioned and obviously impotent prescriptions. The reviewer parted company with the views expressed in the first section on influenza, where the statement is made that "a free current of air is probably the most important single point in the whole treatment." The advice to give a vaccine of pneumococci, streptococci and influenza bacilli in the treatment of lobar pneumonia and

the reasons in favor of this procedure are out of accord with sound practice; and so it goes throughout the book. Better discussions can be found in any reputable textbook.

Lésions du pancréas et troubles fonctionnels pancréatiques. By Marc Bolgert. Price, 45 francs. Pp. 262, with 22 illustrations. Paris: Masson & Cie, 1935.

This is an interesting monograph on pancreatic disease. It is concerned especially with the method of testing the external secretion of the gland as collected by a duodenal tube after the injection of purified secretin. There is a great deal of interesting detailed material, for a complete account of which the original work must be consulted.

Gefässerweiternde Stoffe der Gewebe. By J. H. Gaddum and H. H. Dale. Price, 18 marks. Pp. 200. Leipzig: Georg Thieme, 1936.

This is a systematic discussion of the chemical, pharmacologic and physiologic bearings of "vaso-dilator tissue substances"—histamine, acetylcholine and other substances. The subject matter is concentrated and heavily documented; this makes difficult consecutive reading, but the book is invaluable as a work of reference.

Books Received

THE THEORETICAL POSSIBILITY OF IMMUNIZING THE OLFACTORY MUCOSA AGAINST POLIOMYELITIS VIRUS. By S. Peskind, M.D. Paper. Pp. 22. Cleveland: S. P. Mount Printing Co., 1936.